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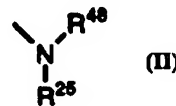
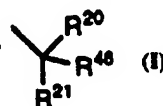
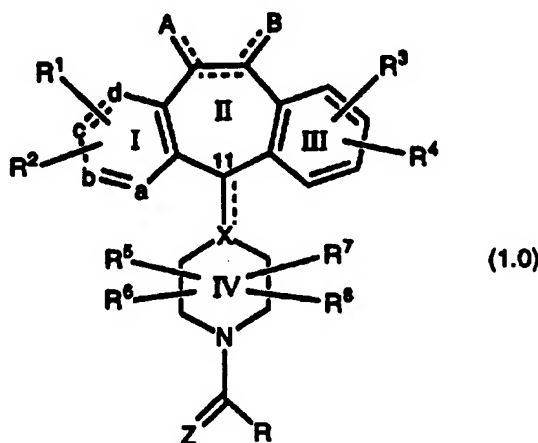
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(54) Title: TRICYCLIC AMIDE AND UREA COMPOUNDS USEFUL FOR INHIBITION OF G-PROTEIN FUNCTION AND FOR TREATMENT OF PROLIFERATIVE DISEASES

(57) Abstract

A method of inhibiting Ras function and therefore inhibiting the abnormal growth of cells is disclosed. The method comprises the administration of a compound of formula (1.0) to a biological system. In particular, the method inhibits the abnormal growth of cells in a mammal such as a human being. Novel compounds wherein X is N, C or OH and R is (I) or (II) are disclosed.



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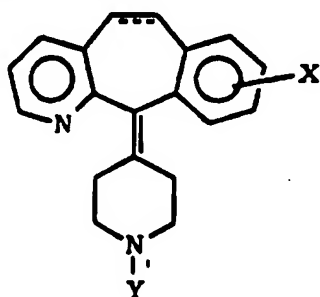
**TRICYCLIC AMIDE AND UREA COMPOUNDS USEFUL FOR
INHIBITION OF G-PROTEIN FUNCTION AND FOR TREATMENT
OF PROLIFERATIVE DISEASES**

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BACKGROUND

International Publication Number WO92/11034, published July 9, 1992, discloses a method of increasing the sensitivity of a tumor to an antineoplastic agent, which tumor is resistant to the antineoplastic agent, by the concurrent administration of the antineoplastic agent and a potentiating agent of the formula:

10



wherein Y' is hydrogen, substituted carboxylate or substituted sulfonyl. Examples of such potentiating agents include 11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridines such as Loratadine.

15

To acquire transforming potential, the precursor of the Ras oncoprotein must undergo farnesylation of the cysteine residue located in a carboxyl-terminal tetrapeptide. Inhibitors of the enzyme that catalyzes this modification, farnesyl protein transferase, have therefore been suggested as anticancer agents for tumors in which Ras contributes to transformation. Mutated, oncogenic forms of ras are frequently found in many human cancers, most notably in more than 50% of colon and pancreatic carcinomas (Kohl et al., Science, Vol. 260, 1834 to 1837, 1993).

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A welcome contribution to the art would be compounds useful for the inhibition of farnesyl protein transferase. Such a contribution is provided by this invention.

SUMMARY OF THE INVENTION

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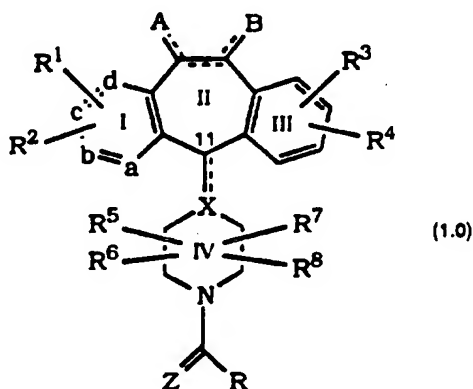
Inhibition of farnesyl protein transferase by tricyclic compounds of this invention has not been reported previously. Thus, this invention provides a method for inhibiting farnesyl protein transferase using tricyclic

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compounds of this invention which: (i) potently inhibit farnesyl protein transferase, but not geranylgeranyl protein transferase I, in vitro; (ii) block the phenotypic change induced by a form of transforming Ras which is a farnesyl acceptor but not by a form of transforming Ras engineered to be a geranylgeranyl acceptor; (iii) block intracellular processing of Ras which is a farnesyl acceptor but not of Ras engineered to be a geranylgeranyl acceptor; and (iv) block abnormal cell growth in culture induced by transforming Ras. Several compounds of this invention have been demonstrated to have anti-tumor activity in animal models.

This invention provides a method for inhibiting the abnormal growth of cells, including transformed cells, by administering an effective amount of a compound of this invention. Abnormal growth of cells refers to cell growth independent of normal regulatory mechanisms (e.g., loss of contact inhibition). This includes the abnormal growth of: (1) tumor cells (tumors) expressing an activated Ras oncogene; (2) tumor cells in which the Ras protein is activated as a result of oncogenic mutation in another gene; and (3) benign and malignant cells of other proliferative diseases in which aberrant Ras activation occurs.

Compounds useful in the claimed methods are represented by Formula 1.0:



or a pharmaceutically acceptable salt or solvate thereof, wherein:

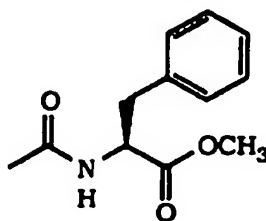
one of a, b, c and d represents N or NR⁹ wherein R⁹ is O⁻, -CH₃ or -(CH₂)_nCO₂H wherein n is 1 to 3, and the remaining a, b, c and d groups represent CR¹ or CR²; or

each of a, b, c, and d are independently selected from CR¹ or CR²;

each R¹ and each R² is independently selected from H, halo, -CF₃, -OR¹⁰ (e.g., -OCH₃), -COR¹⁰, -SR¹⁰ (e.g., -SCH₃ and -SCH₂C₆H₅), -S(O)_tR¹¹ (wherein t is 0, 1 or 2, e.g., -SOCH₃ and -SO₂CH₃), -SCN, -N(R¹⁰)₂, -NR¹⁰R¹¹, -NO₂, -OC(O)R¹⁰, -CO₂R¹⁰, -OCO₂R¹¹, -CN,

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-NHC(O)R¹⁰, -NH₂SO₂R¹⁰, -CONHR¹⁰, -CONHCH₂CH₂OH,
-NR¹⁰COOR¹¹,



- SR¹¹C(O)OR¹¹ (e.g., -SCH₂CO₂CH₃), -SR¹¹N(R⁷⁵)₂ wherein each R⁷⁵
5 is independently selected from H and -C(O)OR¹¹ (e.g.,
-S(CH₂)₂NHC(O)O-t-butyl and -S(CH₂)₂NH₂), benzotriazol-1-yloxy,
tetrazol-5-ylthio, or substituted tetrazol-5-ylthio (e.g., alkyl substituted
tetrazol-5-ylthio such as 1-methyl-tetrazol-5-ylthio), alkynyl, alkenyl or
alkyl, said alkyl or alkenyl group optionally being substituted with halo,
10 -OR¹⁰ or -CO₂R¹⁰;

R³ and R⁴ are the same or different and each independently
represents H, any of the substituents of R¹ and R², or R³ and R⁴ taken
together represent a saturated or unsaturated C₅-C₇ fused ring to the
benzene ring (Ring III);

- 15 R⁵, R⁶, R⁷ and R⁸ each independently represents H, -CF₃, -COR¹⁰,
alkyl or aryl, said alkyl or aryl optionally being substituted with -OR¹⁰,
-SR¹⁰, -S(O)_rR¹¹, -NR¹⁰COOR¹¹, -N(R¹⁰)₂, -NO₂, -COR¹⁰, -OCOR¹⁰,
-OCO₂R¹¹, -CO₂R¹⁰, OPO₃R¹⁰ or one of R⁵, R⁶, R⁷ and R⁸ can be taken
in combination with R⁴⁰ as defined below to represent -(CH₂)_r wherein r
20 is 1 to 4 which can be substituted with lower alkyl, lower alkoxy, -CF₃ or
aryl, or R⁵ is combined with R⁶ to represent =O or =S and/or R⁷ is
combined with R⁸ to represent =O or =S;

R¹⁰ represents H, alkyl, aryl, or aralkyl (e.g., benzyl);

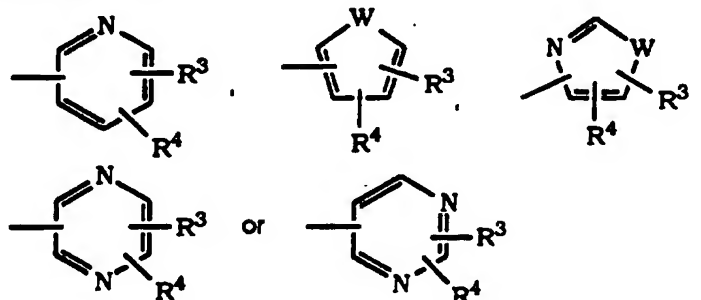
R¹¹ represents alkyl or aryl;

- 25 X represents N, CH or C, which C may contain an optional double
bond (represented by the dotted line) to carbon atom 11;

- the dotted line between carbon atoms 5 and 6 represents an
optional double bond, such that when a double bond is present, A and B
independently represent -NO₂, -R¹⁰, halo, -OR¹¹, -OCO₂R¹¹ or
30 -OC(O)R¹⁰, and when no double bond is present between carbon atoms
5 and 6, A and B each independently represent H₂, -(OR¹¹)₂, H and halo,
dihalo, alkyl and H, (alkyl)₂, -H and -OC(O)R¹⁰, H and -OR¹⁰, =O, aryl and
H, =NOR¹⁰ or -O-(CH₂)_p-O- wherein p is 2, 3 or 4;

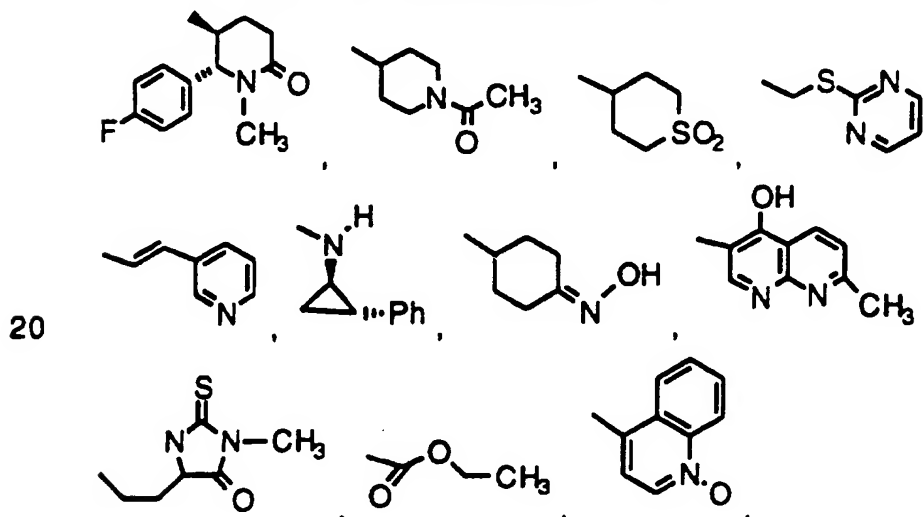
R represents R⁴⁰, R⁴², R⁴⁴, or R⁵⁴, as defined below:

**R⁴⁰ represents H, aryl, alkyl, cycloalkyl, alkenyl, alkynyl or -D
wherein -D represents**

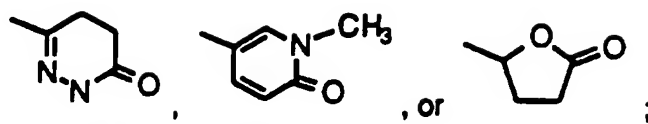
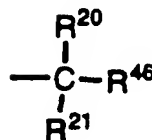


- 5 wherein R³ and R⁴ are as previously defined and W is O, S or NR¹⁰ wherein R¹⁰ is as defined above; said R⁴⁰ cycloalkyl, alkenyl and alkynyl groups being optionally substituted with from 1-3 groups selected from halo, -CON(R¹⁰)₂, aryl, -CO₂R¹⁰, -OR¹², -SR¹², -N(R¹⁰)₂, -N(R¹⁰)CO₂R¹¹, -COR¹², -NO₂ or D, wherein -D, R¹⁰ and R¹¹ are as
10 defined above and R¹² represents R¹⁰, -(CH₂)_mOR¹⁰ or -(CH₂)_qCO₂R¹⁰ wherein R¹⁰ is as previously defined, m is 1 to 4 and q is 0 to 4; said alkenyl and alkynyl R⁴⁰ groups not containing -OH, -SH or -N(R¹⁰)₂ on a carbon containing a double or triple bond respectively; or R⁴⁰ represents phenyl substituted with a group selected from
15 -SO₂NH₂, -NH₂SO₂CH₃, -SO₂NHCH₃, -SO₂CH₃, -SOCH₃, -SCH₃, or -NH₂SO₂CF₃, preferably, said group is located in the para (p-) position of the phenyl ring; or

R⁴⁰ represents a group selected from



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R⁴² represents

wherein R²⁰, R²¹ and R⁴⁶ are each independently selected from the group consisting of:

- (1) H;
- (2) $-(CH_2)_qSC(O)CH_3$ wherein q is 1 to 3 (e.g., $-CH_2SC(O)CH_3$);
- (3) $-(CH_2)_qOSO_2CH_3$ wherein q is 1 to 3 (e.g., $-CH_2OSO_2CH_3$);
- (4) $-OH$;
- (5) $-CS(CH_2)_w(\text{substituted phenyl})$ wherein w is 1 to 3 and the substituents on said substituted phenyl group are the same substituents as described below for said substituted phenyl (e.g., $-C-S-CH_2-4\text{-methoxyphenyl}$);
- (6) $-NH_2$;
- (7) $-NHCBZ$ (wherein CBZ stands for carbonylbenzyloxy--i.e., CBZ represents $-C(O)OCH_2C_6H_5$);
- (8) $-NHC(O)OR^{22}$ wherein R²² is an alkyl group having from 1 to 5 carbon atoms (e.g., R²² is t-butyl thus forming $-NHBOC$ wherein BOC stands for tert-butyloxycarbonyl--i.e., BOC represents $-C(O)OC(CH_3)_3$), or R²² represents phenyl substituted with 1 to 3 alkyl groups (e.g., 4-methylphenyl);
- (9) alkyl (e.g., ethyl);
- (10) $-(CH_2)_k\text{phenyl}$ wherein k is 1 to 6, usually 1 to 4 and preferably 1 (e.g., benzyl);
- (11) phenyl;
- (12) substituted phenyl (i.e., phenyl substituted with from 1 to 3 substituents, preferably one) wherein the substituents are selected from the group consisting of: halo (e.g., Br, Cl, or I, with Br being preferred); NO₂; $-OH$; $-OCH_3$; $-NH_2$; $-NHR^{22}$; $-N(R^{22})_2$; alkyl (e.g., alkyl having from 1 to 3 carbons with methyl being preferred); $-O(CH_2)_t\text{phenyl}$ (wherein t is from 1 to 3 with 1 being preferred); and $-O(CH_2)_t\text{substituted phenyl}$ (wherein t is from 1 to 3 with 1 being preferred); examples of substituted phenyls include, but are not limited to, p-bromophenyl, m-nitrophenyl, o-

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nitrophenyl, m-hydroxyphenyl, o-hydroxyphenyl, methoxyphenyl, p-methylphenyl, m-methylphenyl, and $-\text{OCH}_2\text{C}_6\text{H}_5$;

(13) naphthyl;

(14) substituted naphthyl, wherein the substituents are as defined
5 for substituted phenyl above;

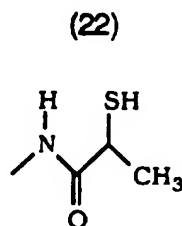
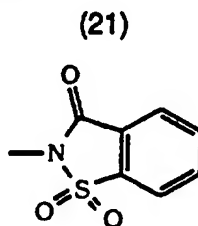
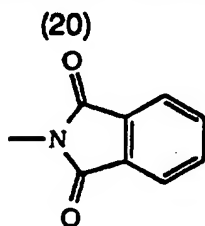
(15) bridged polycyclic hydrocarbons having from 5 to 10 carbon atoms (e.g., adamantyl and norbornyl);

(16) cycloalkyl having from 5 to 7 carbon atoms (e.g., cyclopentyl, and cyclohexyl);

10 (17) heteroaryl (e.g., pyridyl, and pyridyl N-oxide);

(18) hydroxyalkyl (e.g., $-(\text{CH}_2)_v\text{OH}$ wherein v is 1 to 3, such as, for example, $-\text{CH}_2\text{OH}$);

(19) substituted pyridyl or substituted pyridyl N-oxide wherein the substituents are selected from methylpyridyl, morpholinyl, imidazolyl,
15 1-piperidiny, 1-(4-methylpiperazinyl), $-\text{S}(\text{O})_t\text{R}^{11}$, or any of the substituents given above for said substituted phenyl, and said substituents are bound to a ring carbon by replacement of the hydrogen bound to said carbon;



20

(23) $-\text{NHC}(\text{O})-(\text{CH}_2)_k\text{-phenyl}$ or $-\text{NH}(\text{O})-(\text{CH}_2)_k\text{-substitued phenyl}$, wherein said k is as defined above (i.e., 1-6, usually 1-4 and preferably 1);

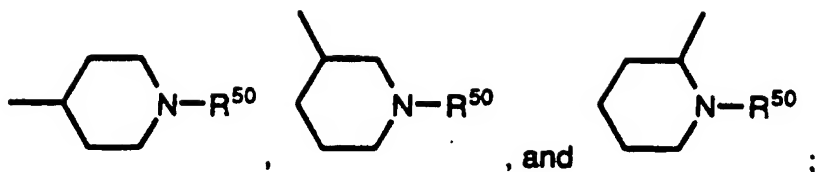
(24) piperidine Ring V:



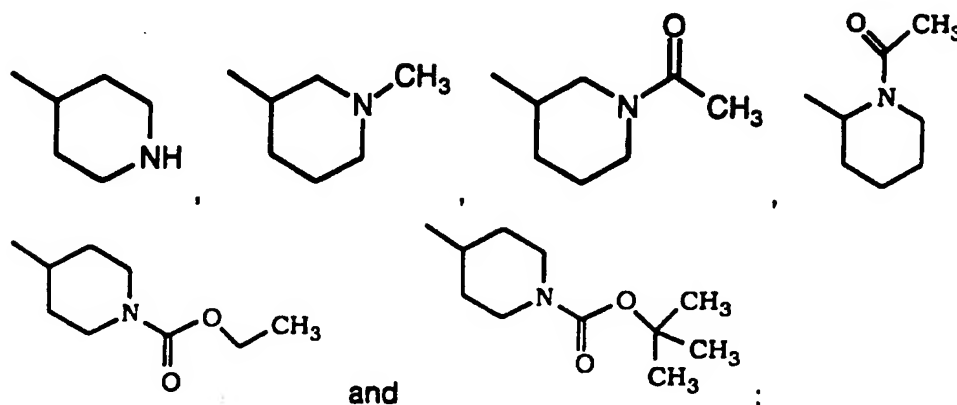
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wherein R^{50} represents H, alkyl (e.g., methyl), alkylcarbonyl (e.g., $\text{CH}_3\text{C}(\text{O})-$), alkyloxycarbonyl (e.g., $-\text{C}(\text{O})\text{O}-t\text{-C}_4\text{H}_9$, $-\text{C}(\text{O})\text{OC}_2\text{H}_5$, and $-\text{C}(\text{O})\text{OCH}_3$), haloalkyl (e.g., trifluoromethyl), or $-\text{C}(\text{O})\text{NH}(\text{R}^{10})$ wherein R^{10} is H or alkyl; Ring V includes

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examples of Ring V include:



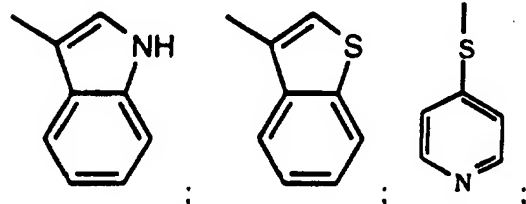
- 5 (25) -NHC(O)CH₂C₆H₅ or -NHC(O)CH₂-substituted-C₆H₅, for example -NHC(O)CH₂-p-hydroxyphenyl, -NHC(O)CH₂-m-hydroxyphenyl, and -NHC(O)CH₂-o-hydroxyphenyl;

(26) -NHC(O)OC₆H₅;

(27)

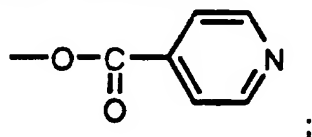
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(30) -OC(O)-heteroaryl, for example



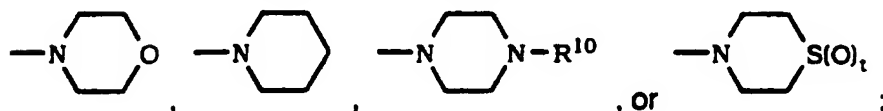
(31) -O-alkyl (e.g., -OCH₃);

(32) -CF₃;

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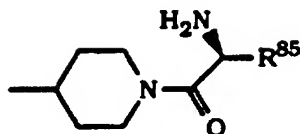
(33) -CN;

(34) a heterocycloalkyl group of the formula



(35) a piperidiny group of the formula

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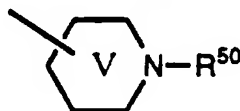


wherein R^{85} is H, alkyl, or alkyl substituted by -OH, -SCH₃ or -SH (preferably -OH or -SCH₃); and

(36) triazolyl; or

5 R^{20} and R^{21} taken together form a =O group and the remaining R^{46} is as defined above; or

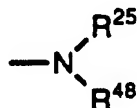
two of R^{20} , R^{21} and R^{46} taken together form piperidine Ring V



wherein Ring V and R^{50} are as defined above;

10 with the proviso R^{46} , R^{20} , and R^{21} are selected such that the carbon atom to which they are bound does not contain more than one heteroatom (i.e., R^{46} , R^{20} , and R^{21} are selected such that the carbon atom to which they are bound contains 0 or 1 heteroatom);

R^{44} represents

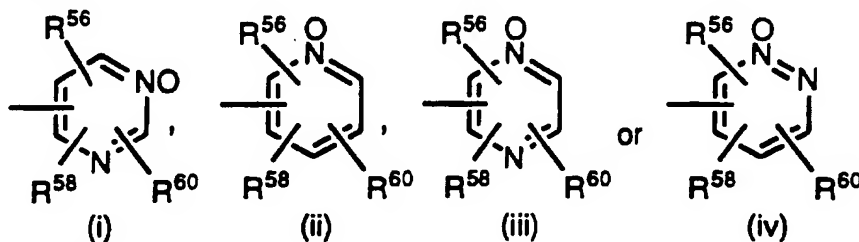


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wherein R^{25} represents heteroaryl (e.g., pyridyl or pyridyl N-oxide), N-methylpiperidinyI or aryl (e.g., phenyl and substituted phenyl); and R^{48} represents H or alkyl (e.g., methyl);

R^{54} represents an N-oxide heterocyclic group of the formula (i), (ii),

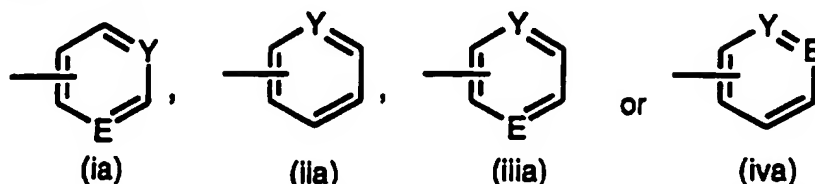
20 (iii) or (iv):



wherein R^{56} , R^{58} , and R^{60} are the same or different and each is independently selected from H, halo, -CF₃, -OR¹⁰, -C(O)R¹⁰, -SR¹⁰, -S(O)_eR¹¹ (wherein e is 1 or 2), -N(R¹⁰)₂, -NO₂, -CO₂R¹⁰, -OCO₂R¹¹, -OCOR¹⁰, alkyl, aryl, alkenyl or alkynyl, which alkyl may be substituted with -OR¹⁰, -SR¹⁰ or -N(R¹⁰)₂ and which alkenyl may be substituted with OR¹¹ or SR¹¹; or

25

R^{54} represents an N-oxide heterocyclic group of the formula (ia), (iia), (iiia) or (iva):



wherein Y represents N^+-O^- and E represents N; or

5 R^{54} represents an alkyl group substituted with one of said N-oxide heterocyclic groups (i), (ii), (iii), (iv), (ia), (iia), (iiia) or (iva);

Z represents O or S such that R can be taken in combination with R^5 , R^6 , R^7 or R^8 as defined above, or R represents R^{40} , R^{42} , R^{44} or R^{54} ; with the proviso that when:

10 (1) R^1 , R^2 , R^3 and R^4 are independently selected from H, halo, $-CF_3$, $-OR^{10}$, $-COR^{10}$, $-SR^{10}$, $-S(O)_tR^{11}$, $-N(R^{10})_2$, $-NO_2$, $-OC(O)R^{10}$, $-CO_2R^{10}$, $-OCO_2R^{11}$, $-CN$, $-NR^{10}COOR^{11}$, $-SR^{11}C(O)OR^{11}$, $-SR^{11}N(R^{75})_2$, benzotriazol-1-yloxy, tetrazol-5-ylthio, substituted tetrazol-5-ylthio, alkynyl, alkenyl or alkyl; or R^1 and R^2 are selected from H, halo,
15 $-CF_3$, $-OR^{10}$, $-COR^{10}$, $-SR^{10}$, $-S(O)_tR^{11}$, $-N(R^{10})_2$, $-NO_2$, $-OC(O)R^{10}$, $-CO_2R^{10}$, $-OCO_2R^{11}$, $-CN$, $-NR^{10}COOR^{11}$, $-SR^{11}C(O)OR^{11}$, $-SR^{11}N(R^{75})_2$, benzotriazol-1-yloxy, tetrazol-5-ylthio, substituted tetrazol-5-ylthio, alkynyl, alkenyl or alkyl, and R^3 and R^4 taken together represent a saturated or unsaturated C_5 - C_7 fused ring to the benzene ring (Ring III);
20 and

(2) the dotted line between carbon atoms 5 and 6 represents an optional double bond, such that when a double bond is present, A and B independently represent $-R^{10}$, halo, $-OR^{11}$, $-OCO_2R^{11}$ or $-OC(O)R^{10}$, and when no double bond is present between carbon atoms 5 and 6, A and B each independently represent H_2 , $-(OR^{11})_2$, H and halo, dihalo,
25 alkyl and H, $(alkyl)_2$, $-H$ and $-OC(O)R^{10}$, H and $-OR^{10}$, $=O$, aryl and H, $=NOR^{10}$ or $-O-(CH_2)_p-O-$ wherein p is 2, 3 or 4;

then R is selected from:

(a) R^{42} wherein at least one of R^{20} , R^{21} or R^{46} is selected
30 from:

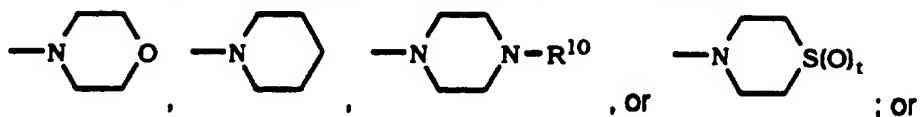
(1) substituted pyridyl or substituted pyridyl N-oxide wherein the substituents are selected from methylpyridyl, morpholinyl, imidazolyl, 1-piperidinyl, 1-(4-methylpiperazinyl), or $-S(O)_tR^{11}$;

(2) $-CN$;

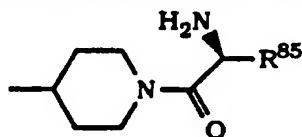
- 10 -

(3) triazolyl;

(4) a heterocycloalkyl group of the formula

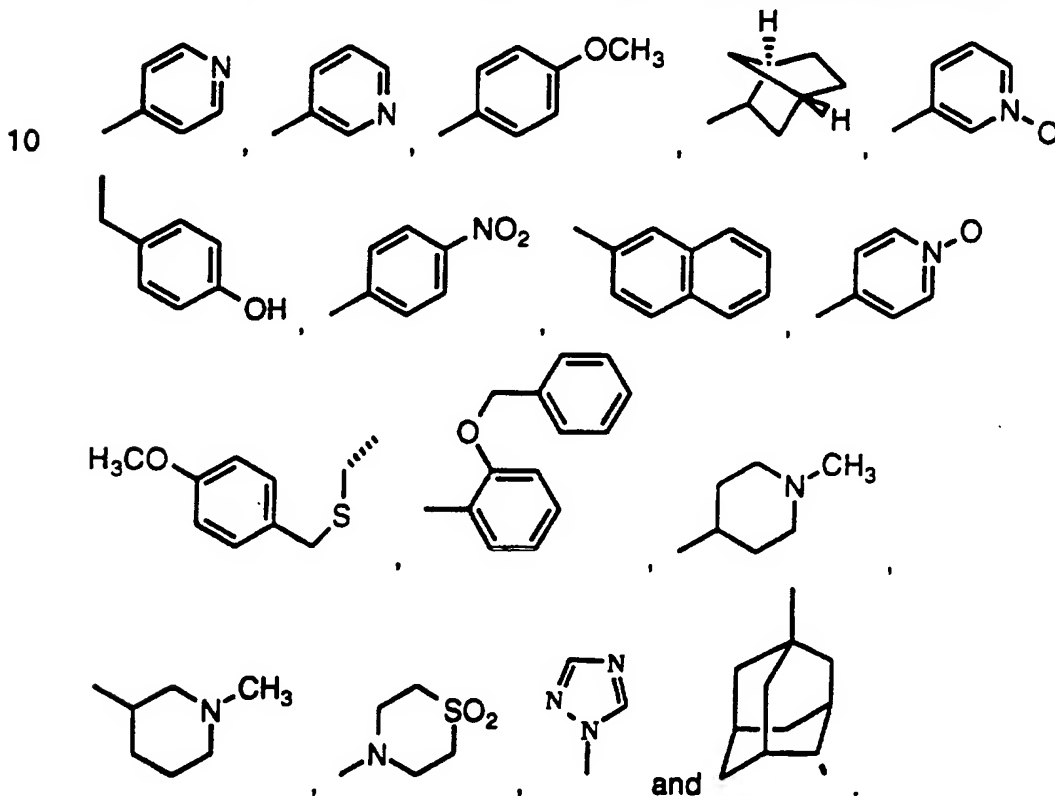
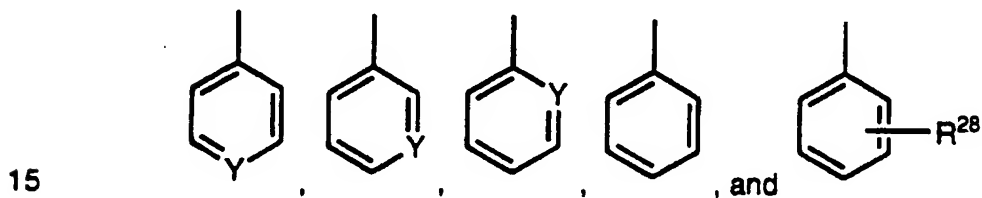


(5) a piperidiny group of the formula



5

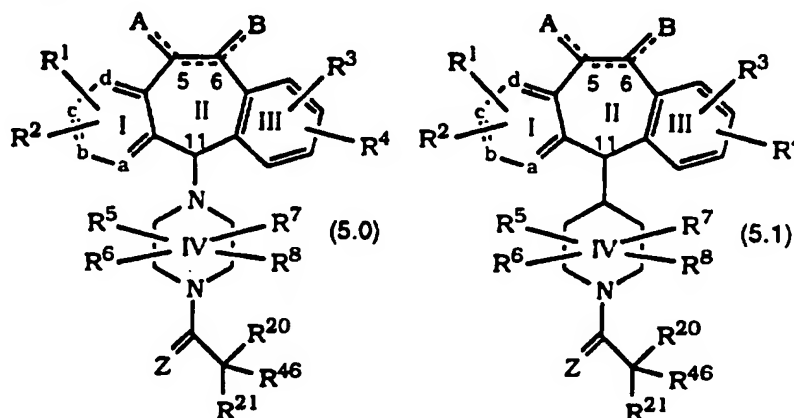
wherein R^{85} is H, alkyl, or alkyl substituted by -OH, -SCH₃ or -SH (preferably -OH or -SCH₃); or

(b) R^{44} wherein R^{25} is N-methylpiperidiny.Examples of R^{20} , R^{21} , and R^{46} for the above formulas include:Examples of R^{25} groups include:

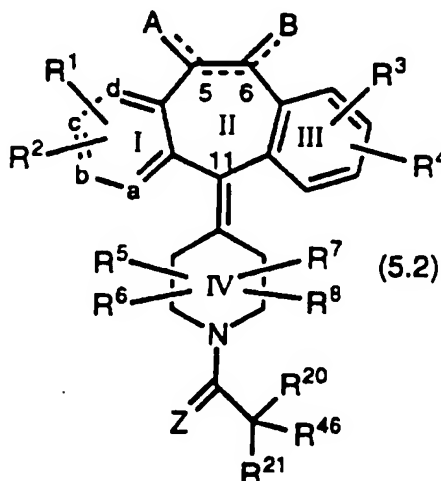
15

wherein Y represents N or NO, R^{28} is selected from the group consisting of: C_1 to C_4 alkyl, halo, hydroxy, NO_2 , amino ($-NH_2$), $-NHR^{30}$, and $-N(R^{30})_2$ wherein R^{30} represents C_1 to C_6 alkyl.

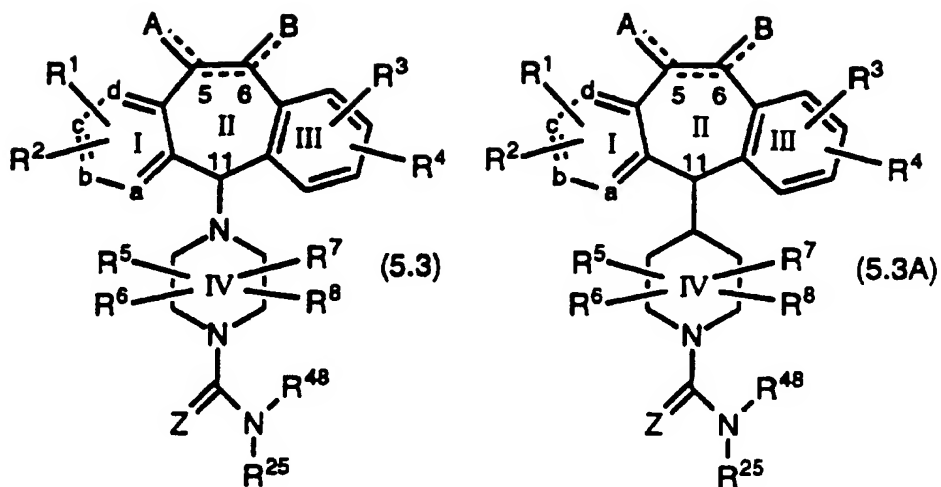
- This invention also provides novel compounds of Formula 1.0
 5 having the Formula 5.0. This invention further provides novel compounds of Formula 1.0 having the Formula 5.1. Additionally, this invention provides novel compounds of Formula 1.0 having the Formula 5.2. These formulas are identified below and all substituents are as defined for Formula 1.0:



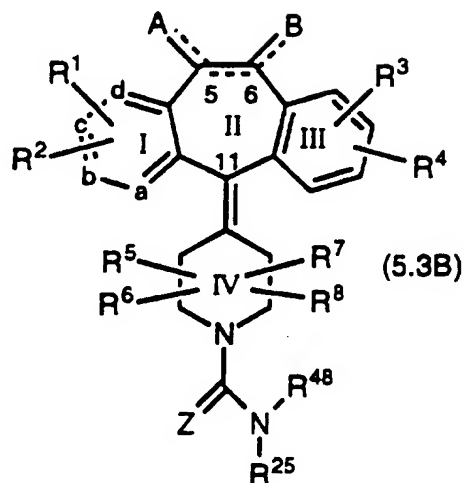
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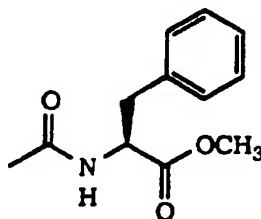
This invention further provides novel compounds of Formula 1.0 having the formula:



or



- wherein a, b, c, d, R⁵, R⁶, R⁷, R⁸, A, B and Z are as defined for Formula 1.0; each R¹ and each R² is independently selected from H, halo, -CF₃,
 5 -OR¹⁰, -COR¹⁰, -SR¹⁰, -S(O)_tR¹¹ (wherein t is 0, 1 or 2), -SCN, -N(R¹⁰)₂,
 -NR¹⁰R¹¹, -NO₂, -OC(O)R¹⁰, -CO₂R¹⁰, -OCO₂R¹¹, -CN, -NHC(O)R¹⁰,
 -NHSO₂R¹⁰, -CONHR¹⁰, -CONHCH₂CH₂OH, -NR¹⁰COOR¹¹,
 -SR¹¹C(O)OR¹¹,



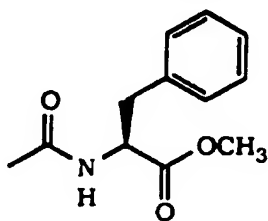
- 10 -SR¹¹N(R⁷⁵)₂ (wherein each R⁷⁵ is independently selected from H and
 -C(O)OR¹¹), benzotriazol-1-yloxy, tetrazol-5-ylthio, or substituted tetrazol-
 5-ylthio, alkynyl, alkenyl or alkyl, said alkyl or alkenyl group optionally

- 13 -

being substituted with halo, $-OR^{10}$ or $-CO_2R^{10}$; R^3 and R^4 are the same or different and each independently represents H, any of the substituents of R^1 and R^2 , or R^3 and R^4 taken together represent a saturated or unsaturated C_5 - C_7 fused ring to the benzene ring; R^{25} represents
 5 heteroaryl, N-methylpiperidinyl or aryl (preferably R^{25} represents heteroaryl); and R^{48} represents H or alkyl; and

with the proviso that:

(1) when R^{25} is selected from heteroaryl or aryl then: (a) at least one of said R^1 , R^2 , R^3 and R^4 groups is selected from $-SCN$, $-NR^{10}R^{11}$,
 10 $-NHC(O)R^{10}$, $-NHSO_2R^{10}$, $-CONHR^{10}$, $-CONHCH_2CH_2OH$, or



; or

(b) the double bond between carbon atoms 5 and 6 is present and at least one of A and B represents $-NO_2$; and

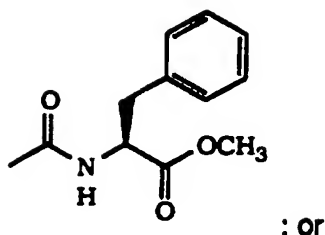
(2) when R^{25} is N-methylpiperidinyl selected from 3-N-methyl-
 15 piperidinyl or 4-N-methylpiperidinyl then R^1 and R^2 are not H, halo, $-CF_3$, benzotriazol-1-yloxy or lower alkyl when: (a) R^3 and R^4 are selected from H and halo; and (b) the double bond between carbon atoms 5 and 6 is present and A and B are selected from H, lower alkyl or lower alkoxy, or the double bond between carbon atoms 5 and 6 is absent and A and B are selected from H_2 , $(-H$ and $-OH)$ or $=O$; and (c) R^5 , R^6 , R^7 , and R^8 are
 20 H; and (d) Z is O.

Compounds of 5.3, 5.3A and 5.3B also include compounds wherein when R^{25} is N-methylpiperidinyl selected from 3-N-methyl-
 25 piperidinyl or 4-N-methylpiperidinyl then R^1 and R^2 are not H, halo, $-CF_3$, benzotriazol-1-yloxy or lower alkyl.

Compounds of 5.3, 5.3A and 5.3B further include compounds wherein when R^{25} is N-methylpiperidinyl then R^1 and R^2 are not H, halo, $-CF_3$, benzotriazol-1-yloxy or lower alkyl.

Compounds of 5.3, 5.3A and 5.3B also include compounds
 30 wherein when R^{25} is N-methylpiperidinyl then: (1) at least one of said R^1 , R^2 , R^3 and R^4 is selected from: $-SCN$, $-NR^{10}R^{11}$, $-NHC(O)R^{10}$, $-NHSO_2R^{10}$, $-CONHR^{10}$, $-CONHCH_2CH_2OH$, or

- 14 -



(2) the double bond between carbon atoms 5 and 6 is present and at least one of A and B represents -NO₂.

This invention also provides a method for inhibiting tumor growth by administering an effective amount of the tricyclic compounds, described herein, to a mammal (e.g., a human) in need of such treatment. In particular, this invention provides a method for inhibiting the growth of tumors expressing an activated Ras oncogene by the administration of an effective amount of the above described compounds. Examples of tumors which may be inhibited include, but are not limited to, lung cancer (e.g., lung adenocarcinoma), pancreatic cancers (e.g., pancreatic carcinoma such as, for example, exocrine pancreatic carcinoma), colon cancers (e.g., colorectal carcinomas, such as, for example, colon adenocarcinoma and colon adenoma), myeloid leukemias (for example, acute myelogenous leukemia (AML)), thyroid follicular cancer, myelodysplastic syndrome (MDS), bladder carcinoma and epidermal carcinoma.

It is believed that this invention also provides a method for inhibiting proliferative diseases, both benign and malignant, wherein Ras proteins are aberrantly activated as a result of oncogenic mutation in other genes-- i.e., the Ras gene itself is not activated by mutation to an oncogenic form-- with said inhibition being accomplished by the administration of an effective amount of the tricyclic compounds described herein, to a mammal (e.g., a human) in need of such treatment. For example, the benign proliferative disorder neurofibromatosis, or tumors in which Ras is activated due to mutation or overexpression of tyrosine kinase oncogenes (e.g., neu, src, abl, lck, and fyn), may be inhibited by the tricyclic compounds described herein.

The compounds of this invention inhibit farnesyl protein transferase and the farnesylation of the oncogene protein Ras. This invention further provides a method of inhibiting ras farnesyl protein transferase, in mammals, especially humans, by the administration of an effective amount of the tricyclic compounds described above. The administration of the

compounds of this invention to patients, to inhibit farnesyl protein transferase, is useful in the treatment of the cancers described above.

The tricyclic compounds useful in the methods of this invention inhibit the abnormal growth of cells. Without wishing to be bound by theory, it is believed that these compounds may function through the inhibition of G-protein function, such as ras p21, by blocking G-protein isoprenylation, thus making them useful in the treatment of proliferative diseases such as tumor growth and cancer. Without wishing to be bound by theory, it is believed that these compounds inhibit ras farnesyl protein transferase, and thus show antiproliferative activity against ras transformed cells.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the following terms are used as defined below unless otherwise indicated:

MH⁺-represents the molecular ion plus hydrogen of the molecule in the mass spectrum;

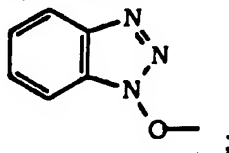
Bu-represents butyl;

Et-represents ethyl;

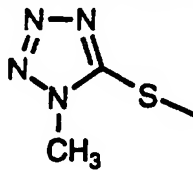
Me-represents methyl;

Ph-represents phenyl;

benzotriazol-1-yloxy represents



1-methyl-tetrazol-5-ylthio represents



alkyl-(including the alkyl portions of alkoxy, alkylamino and dialkylamino)-represents straight and branched carbon chains and contains from one to twenty carbon atoms, preferably one to six carbon atoms;

alkanediyl-represents a divalent, straight or branched hydrocarbon chain having from 1 to 20 carbon atoms, preferably 1 to 6 carbon atoms, the two available bonds being from the same or different carbon atoms thereof, e.g., methylene, ethylene, ethylidene,

-CH₂CH₂CH₂-, -CH₂CHCH₃-, -CHCH₂CH₃-, etc.

cycloalkyl-represents saturated carbocyclic rings branched or unbranched of from 3 to 20 carbon atoms, preferably 3 to 7 carbon atoms;

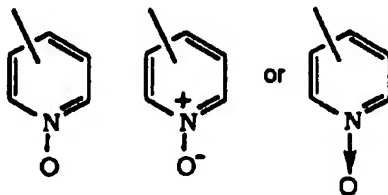
heterocycloalkyl-represents a saturated, branched or unbranched carbocyclic ring containing from 3 to 15 carbon atoms, preferably from 4 to 6 carbon atoms, which carbocyclic ring is interrupted by 1 to 3 hetero groups selected from -O-, -S- or -NR¹⁰-(suitable heterocycloalkyl groups including 2- or 3-tetrahydrofuranyl, 2- or 3- tetrahydrothienyl, 2-, 3- or 4-piperidiny, 2- or 3-pyrrolidiny, 2- or 3-piperiziny, 2- or 4-dioxany, etc.);

alkenyl-represents straight and branched carbon chains having at least one carbon to carbon double bond and containing from 2 to 12 carbon atoms, preferably from 2 to 6 carbon atoms and most preferably from 3 to 6 carbon atoms;

alkynyl-represents straight and branched carbon chains having at least one carbon to carbon triple bond and containing from 2 to 12 carbon atoms, preferably from 2 to 6 carbon atoms;

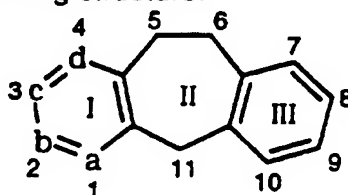
aryl (including the aryl portion of aryloxy and aralkyl)-represents a carbocyclic group containing from 6 to 15 carbon atoms and having at least one aromatic ring (e.g., aryl is a phenyl ring), with all available substitutable carbon atoms of the carbocyclic group being intended as possible points of attachment, said carbocyclic group being optionally substituted (e.g., 1 to 3) with one or more of halo, alkyl, hydroxy, alkoxy, phenoxy, CF₃, amino, alkylamino, dialkylamino, -COOR¹⁰ or -NO₂; and

halo-represents fluoro, chloro, bromo and iodo; and
heteroaryl-represents cyclic groups, optionally substituted with R³ and R⁴, having at least one heteroatom selected from O, S or N, said heteroatom interrupting a carbocyclic ring structure and having a sufficient number of delocalized pi electrons to provide aromatic character, with the aromatic heterocyclic groups preferably containing from 2 to 14 carbon atoms, e.g., triazolyl, 2-, 3- or 4-pyridyl or pyridyl N-oxide (optionally substituted with R³ and R⁴), wherein pyridyl N-oxide can be represented as:



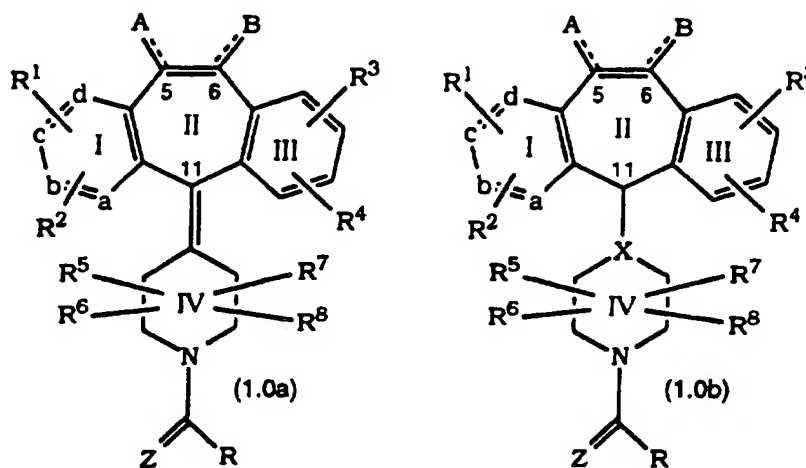
- The following solvents and reagents are referred to herein by the abbreviations indicated: tetrahydrofuran (THF); ethanol (EtOH); methanol (MeOH); acetic acid (HOAc or AcOH); ethyl acetate (EtOAc); N,N-dimethylformamide (DMF); trifluoroacetic acid (TFA); trifluoroacetic anhydride (TFAA); 1-hydroxybenzotriazole (HOBT); m-chloroperbenzoic acid (MCPBA); triethylamine (Et₃N); diethyl ether (Et₂O); ethyl chloroformate (ClCO₂Et); and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (DEC).

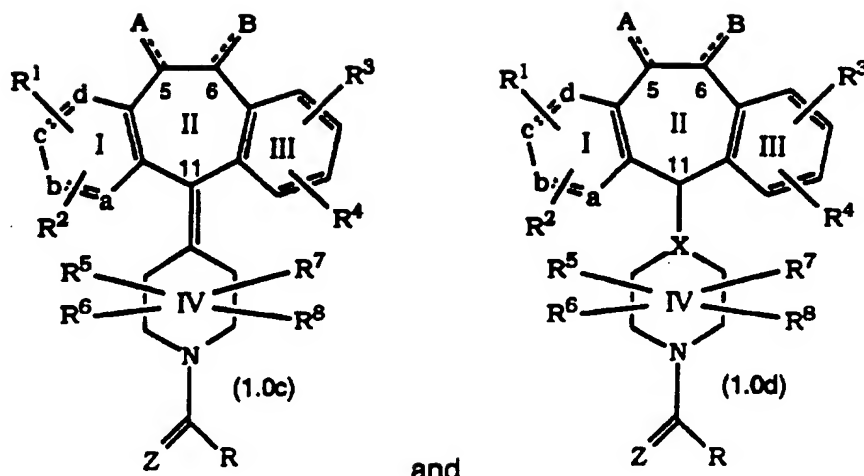
- Reference to the position of the substituents R¹, R², R³, and R⁴ is based on the numbered ring structure:



For example, R¹ can be at the C-4 position and R² can be at the C-2 or C-3 position. Also, for example, R³ can be at the C-8 position and R⁴ can be at the C-9 position.

- Representative structures of Formula 1.0 include but are not limited to:





Preferably, for the compounds of Formula 1.0 (including 1.0a to 1.0d):

each of a, b, c, and d are C (carbon); or

- 5 one of a, b, c and d (most preferably a) represents N or NO, most preferably N, and the remaining a, b, c and d groups represent CR¹ or CR²;

- each R¹ and each R² is independently selected from H, halo (e.g., Cl, Br and F), -CF₃, -OR¹⁰ (e.g., hydroxy and alkoxy (e.g., -OCH₃)), alkyl (e.g., methyl and t-butyl, said alkyl group being optionally substituted with halo), benzotriazol-1-yloxy, -S(O)_tR¹¹ (e.g., -SCH₂CH₃), -SR¹¹C(O)OR¹¹ (e.g., -SCH₂CO₂CH₃), -SR¹⁰ (e.g., R¹⁰ represents -CH₂C₆H₅) and 1-methyl-tetrazol-5-ylthio; most preferably R¹ and R² are independently H, halo, -CF₃, lower alkyl (e.g., C₁ to C₄, more preferably methyl) or
- 10 benzotriazol-1-yloxy; more preferably R¹ is Cl or H, and R² is H, Cl or Br; still more preferably R¹ is at the C-4 position, and R² is at the C-3 position; even more preferably R² is Br, Cl or I;

- R³ and R⁴ are the same or different and each independently represents H, halo, -CF₃, -OR¹⁰, -COR¹⁰, -SR¹⁰, -S(O)_tR¹¹ (wherein t is 0, 1 or 2), -N(R¹⁰)₂, -NO₂, -OC(O)R¹⁰, -CO₂R¹⁰, -OCO₂R¹¹, -C(O)NHR¹⁰, -CN, -NR¹⁰COOR¹¹, alkynyl, alkenyl or alkyl, said alkyl or alkenyl group optionally being substituted with halo, -OR¹⁰ or -CO₂R¹⁰; most preferably R³ and R⁴ independently represent H, halo, -CF₃, -OR¹⁰ or alkyl (said alkyl group being optionally substituted with halo); more preferably R³ and R⁴ independently represent H or halo (e.g., Cl, Br, or F); even more
- 20 preferably R³ is at the C-8 position and R⁴ is at the C-9 position; still more preferably R³ is Cl at the C-8 position and R⁴ is H at the C-9 position;
- 25

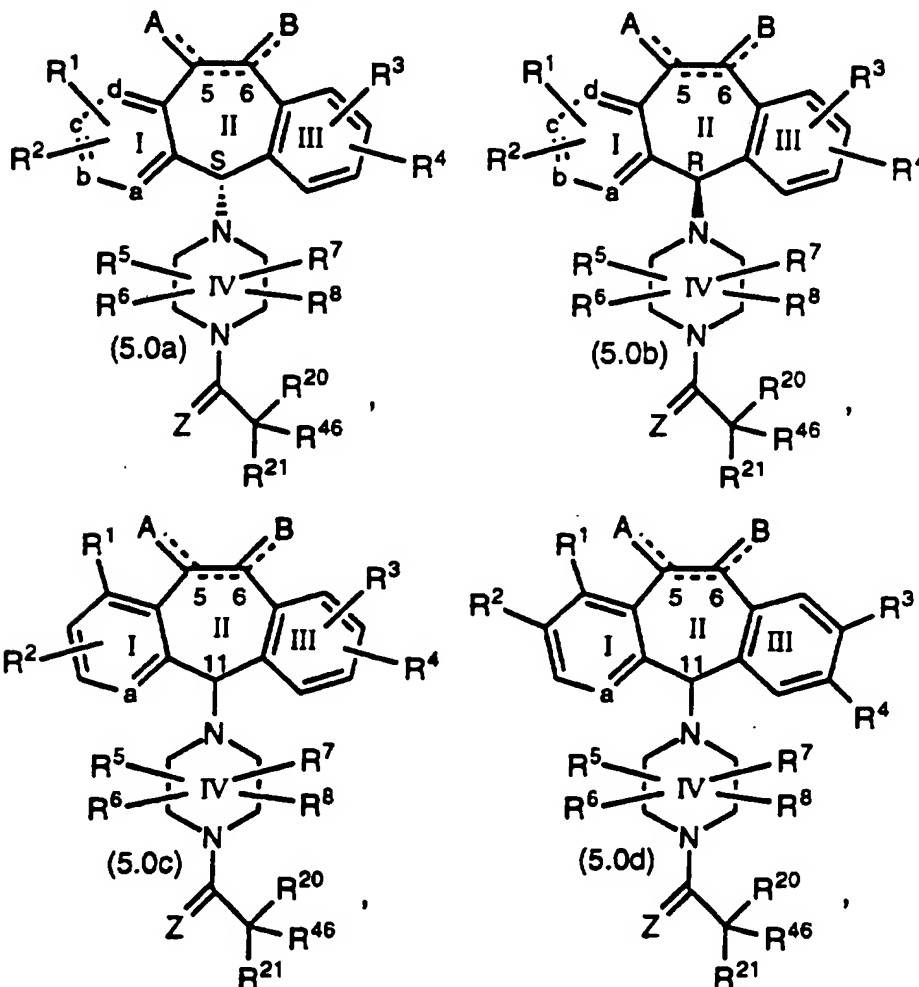
R^5 , R^6 , R^7 and R^8 each independently represents H, $-CF_3$ or alkyl (said alkyl optionally being substituted with $-OR^{10}$); most preferably R^5 , R^6 , R^7 and R^8 independently represent H and alkyl, and more preferably H;

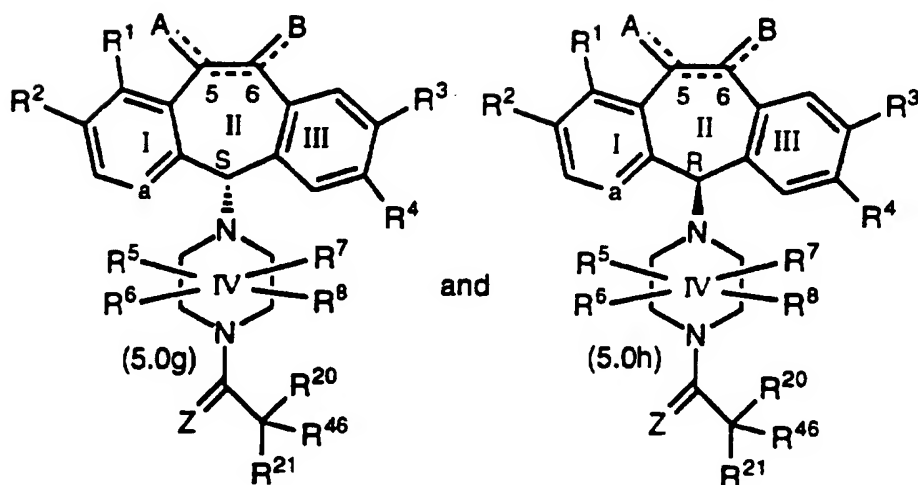
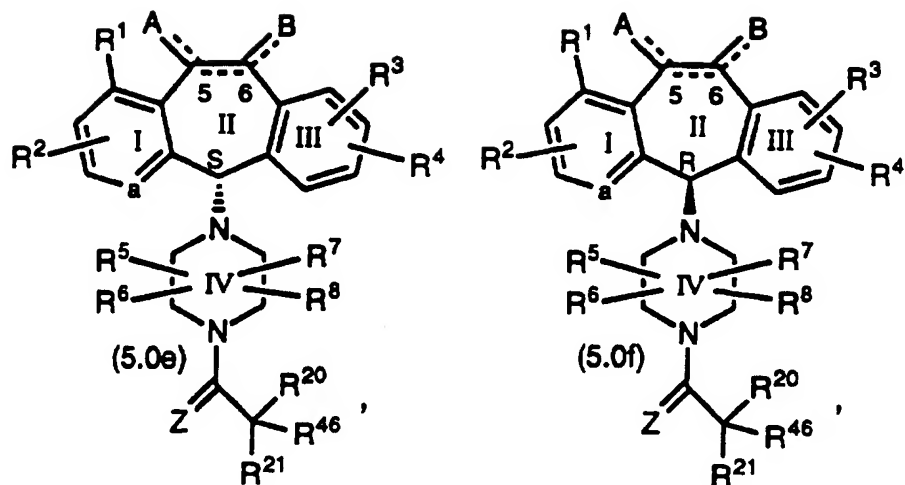
- 5 when the optional double bond between carbon atoms 5 and 6 is present, A and B independently represent H, $-R^{10}$ or $-OR^{10}$, most preferably H, lower alkyl (C_1 to C_4) and alkyloxy (i.e., R^{10} represents alkyl), more preferably H and $-OH$, and still more preferably H; and when no double bond is present between carbon atoms 5 and 6, A and B each
- 10 independently represent H_2 , $-(OR^{10})_2$, alkyl and H, $(alkyl)_2$, $-H$ and $-OR^{10}$ or $=O$, most preferably H_2 , $-H$ and $-OH$, or $=O$, and more preferably A represents H_2 and B represents H_2 or $=O$;

R represents R^{42} or R^{44} ; and

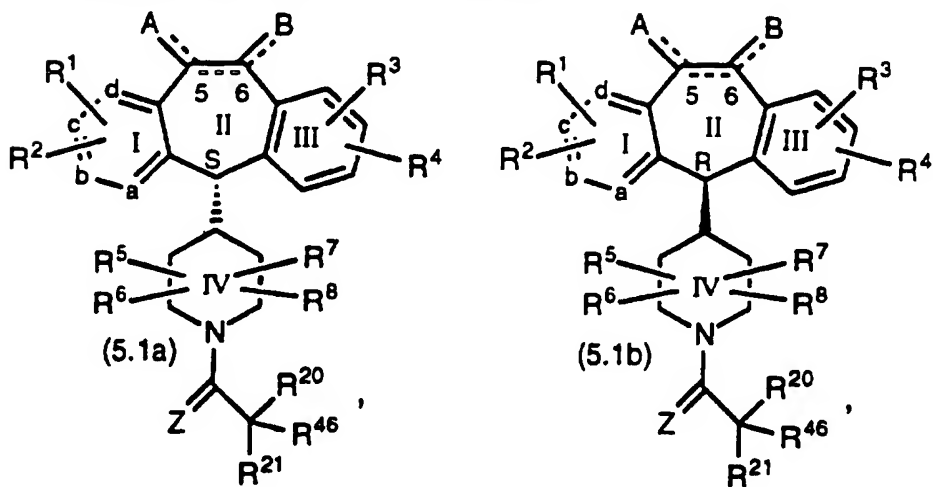
Z represents O or S, and most preferably O.

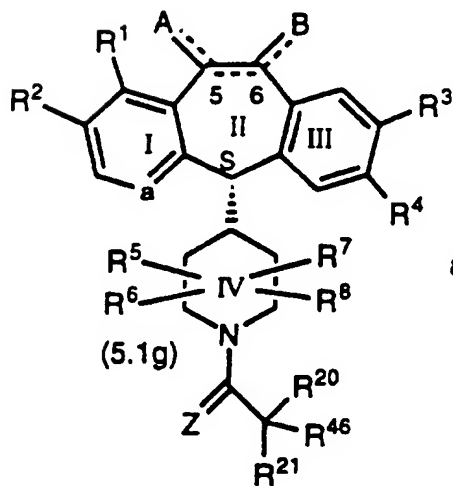
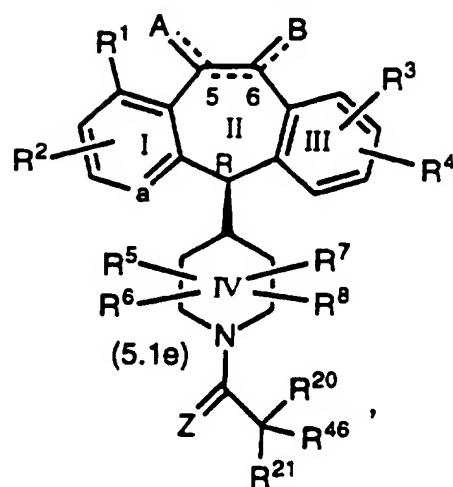
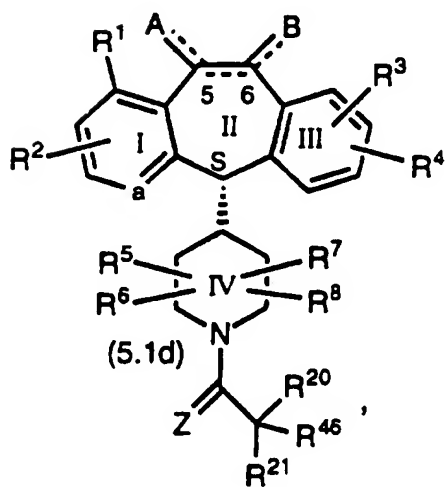
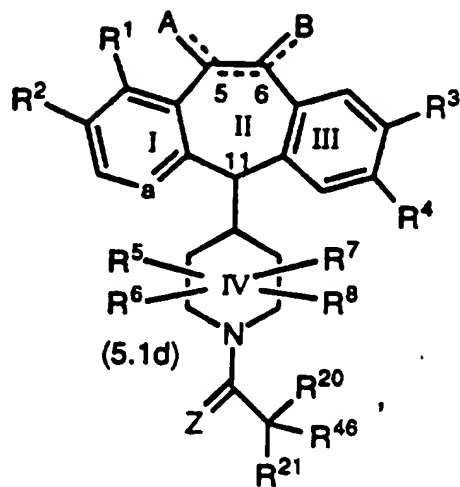
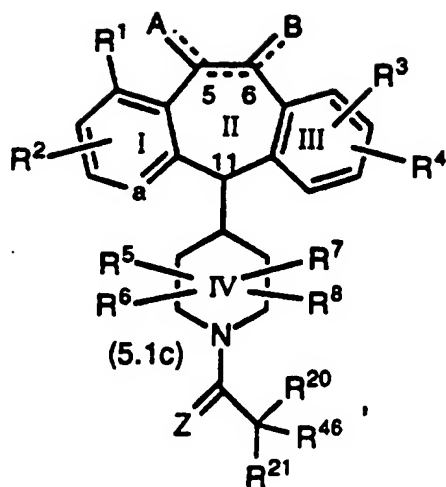
- 15 Compounds of Formula 5.0 include:



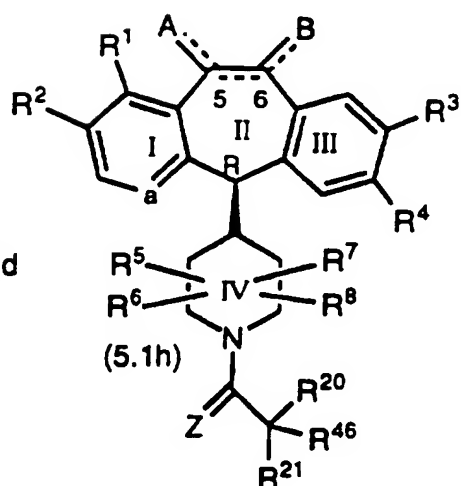


Compounds of Formula 5.1 include:

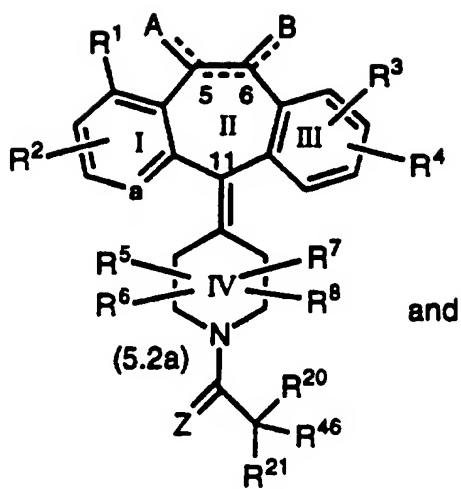




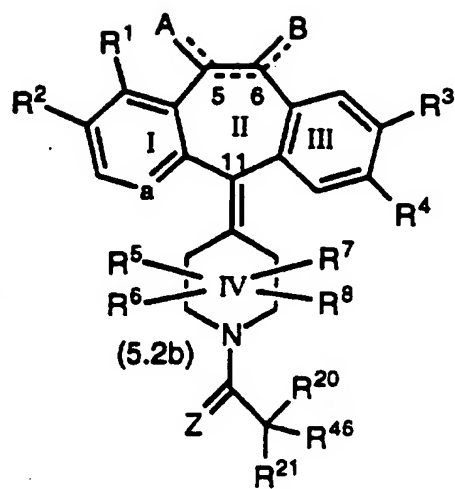
and



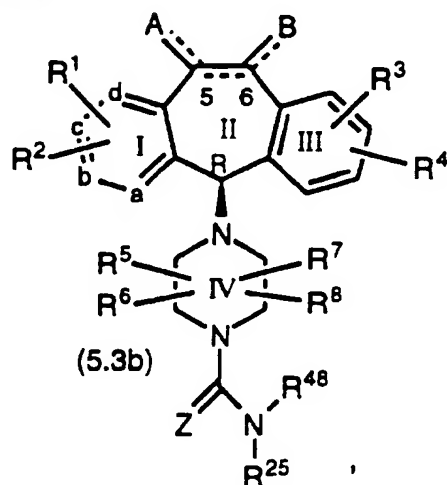
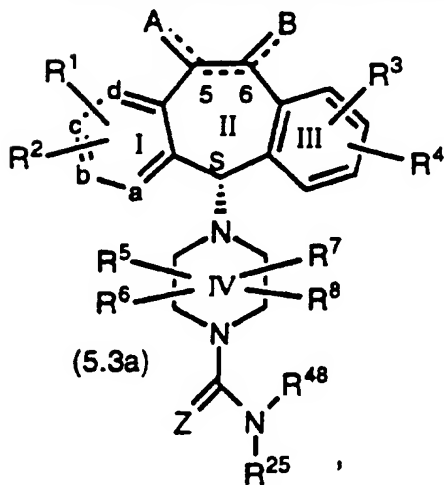
Compounds of Formula 5.2 additionally include:

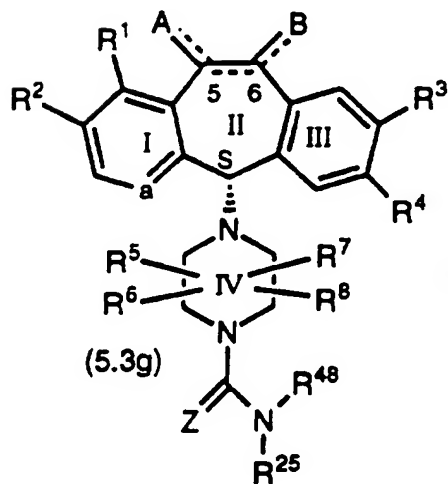
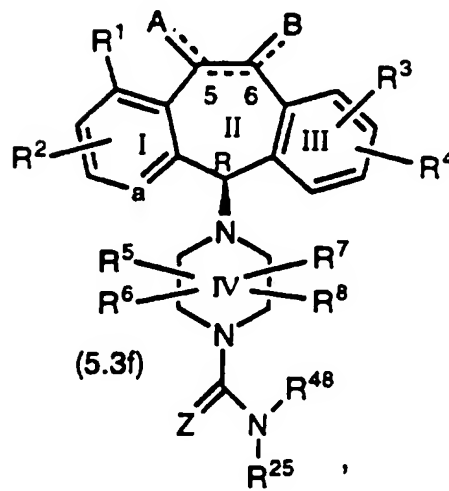
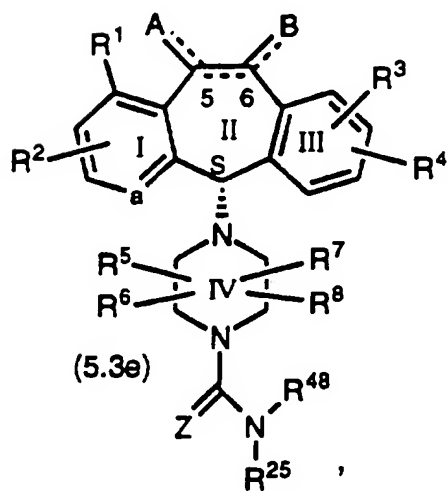
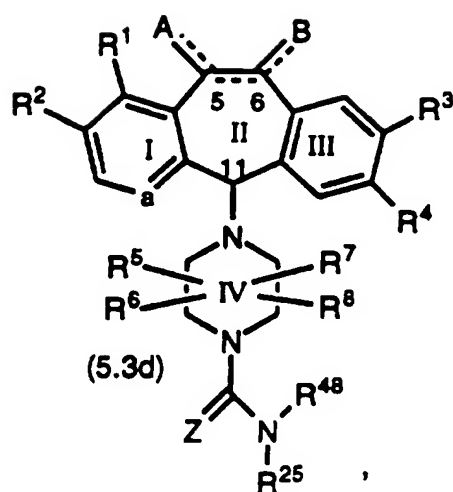
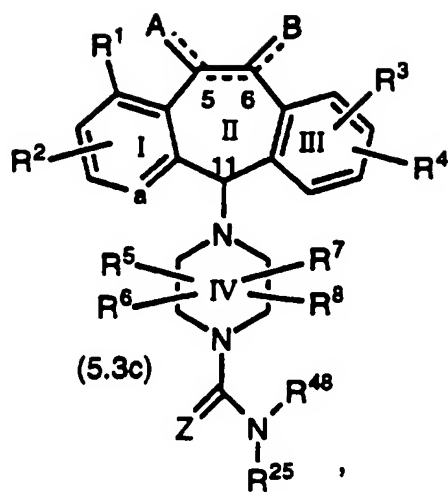


and

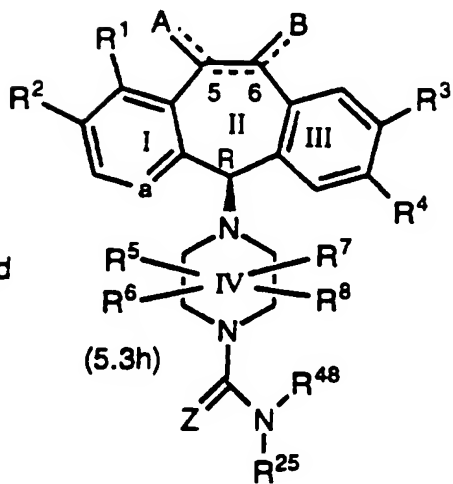


Compounds of Formula 5.3 include:

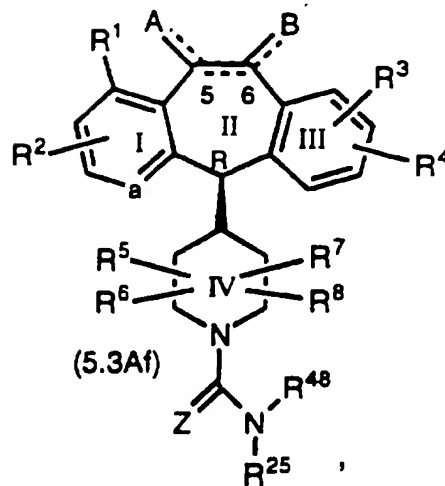
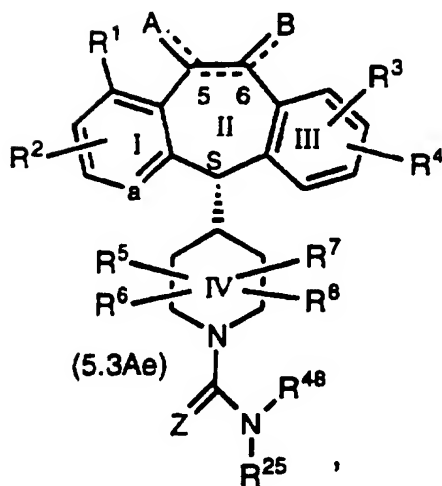
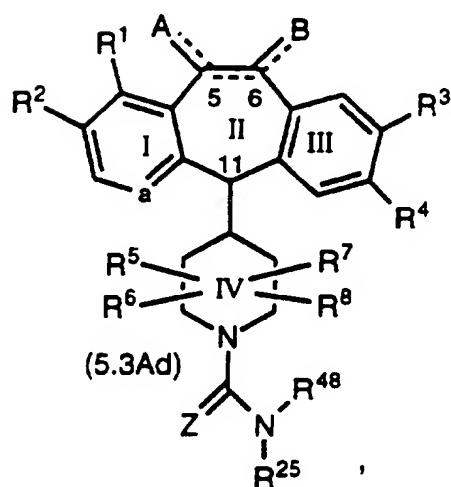
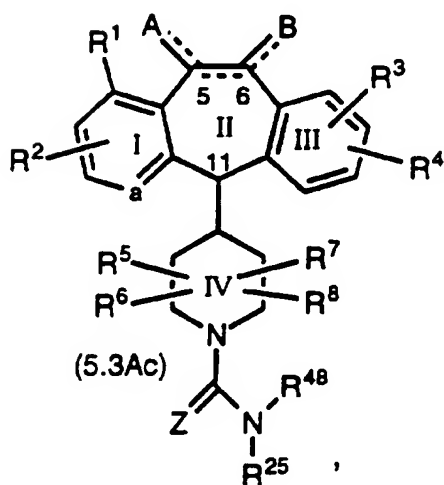
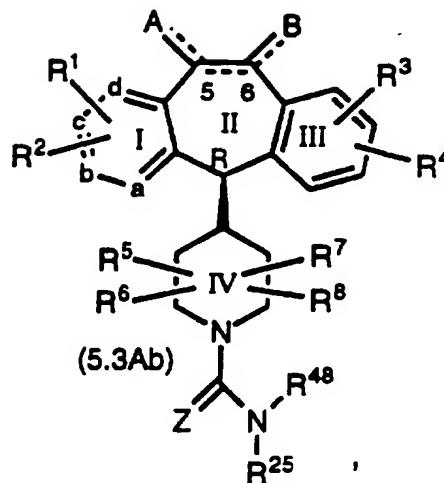
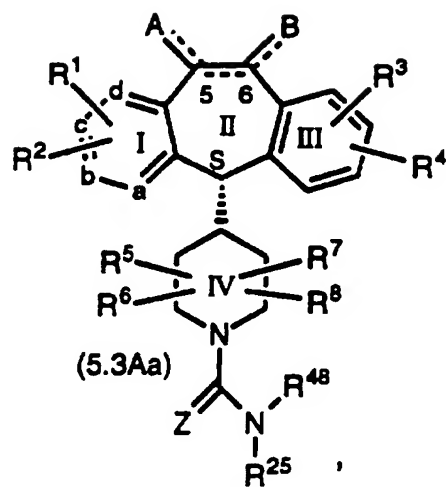


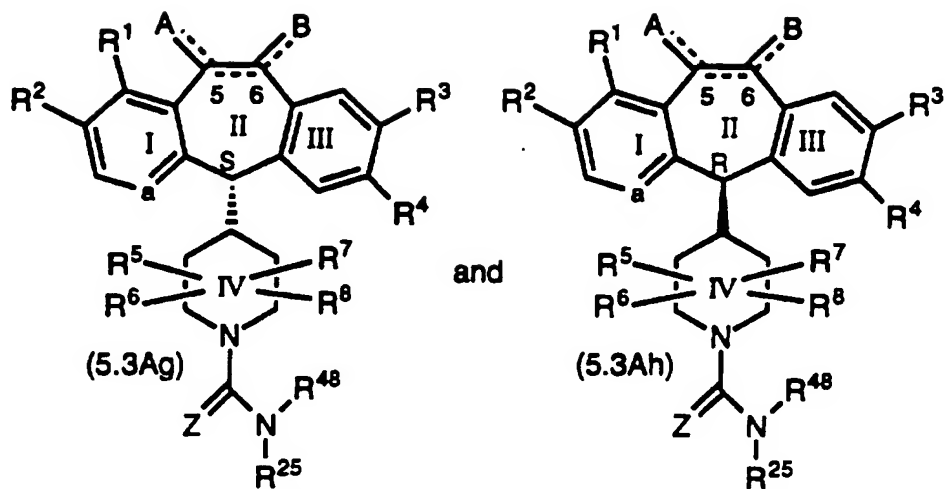


and



Compounds of formula 5.3A include:





For the compounds of Formulas 5.0, 5.0a-5.0h, 5.1, 5.1a-5.1h, 5.2, and 5.2a-5.2b the definitions of the substituents are as defined for Formula 1.0. For the compounds of Formulas 5.3a-5.3h, 5.3A, and 5.3Aa-5.3Ah, the definitions of the substituents are as defined for Formulas 5.3, 5.3A and 5.3B.

Preferably, for compounds of Formulas 5.0, 5.0a-5.0h, 5.1, 5.1a-5.1h, 5.2, and 5.2a-5.2b, R⁴⁶ is selected from piperidine Ring V, heteroaryl, phenyl, substituted phenyl, substituted pyridyl or substituted pyridyl N-oxide, and R²⁰ and R²¹ are independently selected from H or alkyl. Most preferably, R⁴⁶ is pyridyl, pyridyl N-oxide or piperidine Ring V. More preferably, R⁴⁶ is pyridyl, pyridyl N-oxide or piperidine Ring V and both R²⁰ and R²¹ are hydrogen or both R²⁰ and R²¹ are alkyl (still more preferably methyl).

Even more preferably, R⁴⁶ is selected from 3-pyridyl, 4-pyridyl, 3-pyridyl N-oxide, 4-pyridyl N-oxide, 4-N-methylpiperidinyl, 3-N-methylpiperidinyl, 4-N-acetylpiperidinyl or 3-N-acetylpiperidinyl, and both R²⁰ and R²¹ are hydrogen or both R²⁰ and R²¹ are alkyl (still even more preferably methyl). Even still more preferably, R⁴⁶ is selected from 3-pyridyl, 3-pyridyl N-oxide, 4-pyridyl, and 4-pyridyl N-oxide, and both R²⁰ and R²¹ are hydrogen or both R²⁰ and R²¹ are methyl.

For compounds of Formulas 5.0, 5.0a-5.0h, 5.1, 5.1a-5.1h, 5.2, and 5.2a-5.2b, when R¹, R², R³, R⁴, A and B are selected as described in the proviso at the end of the definition of Formula 1.0, then R⁴⁶ is preferably selected from: triazolyl, 1-N-methylpiperazinyl, 1-piperazinyl or a heterocycloalkyl group of the formula

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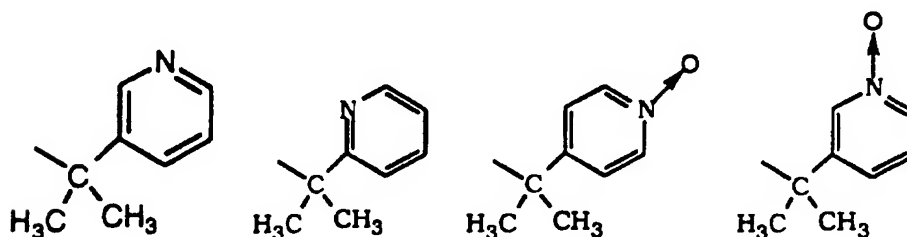
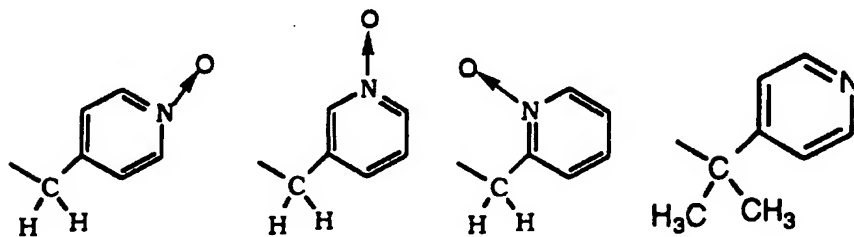
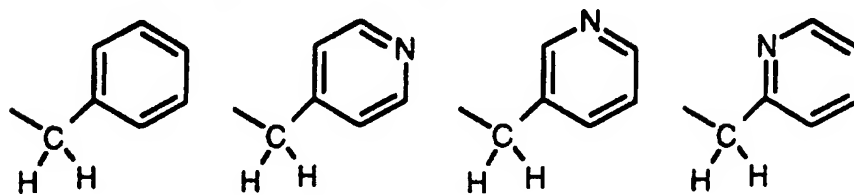


with 1-N-methylpiperaziny, 1-piperaziny, or a heterocycloalkyl group of the formula

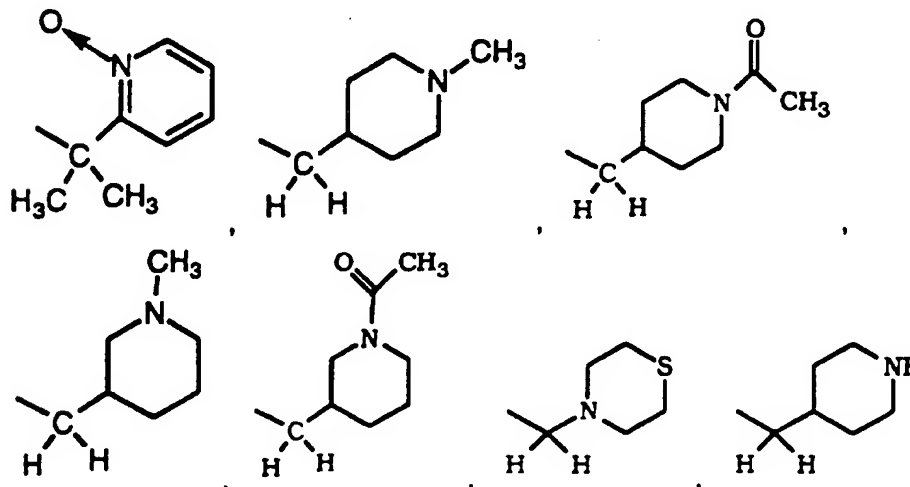


5 being more preferred.

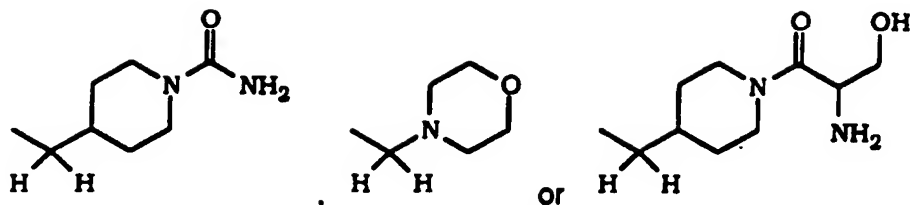
Examples of the R⁴² groups include:



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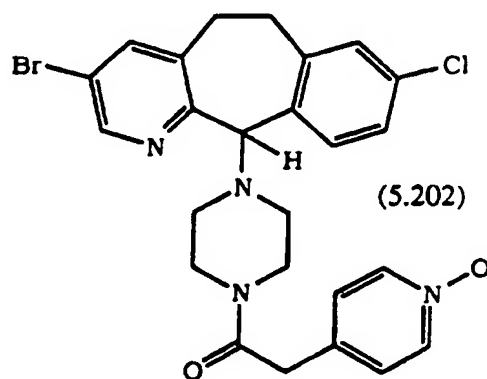
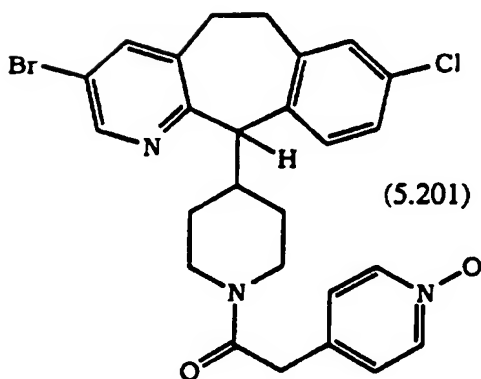
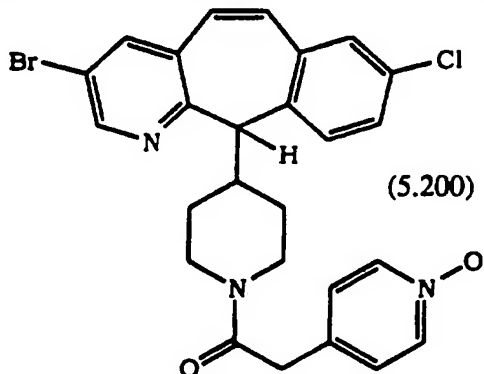


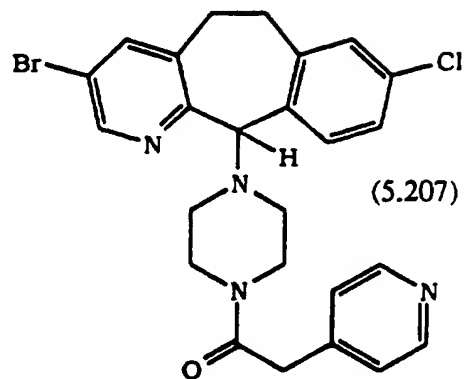
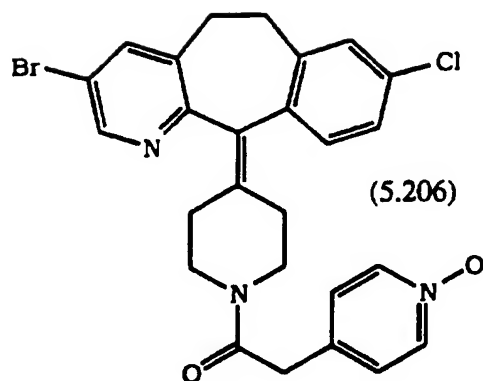
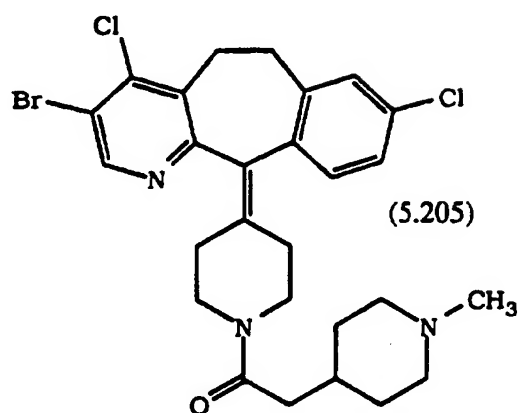
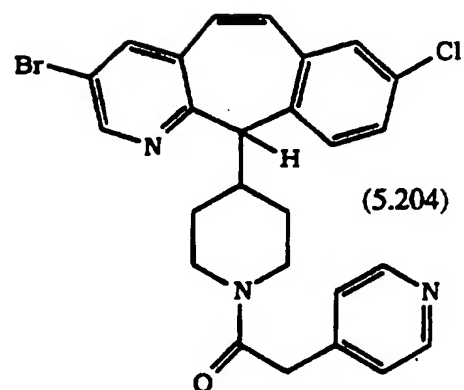
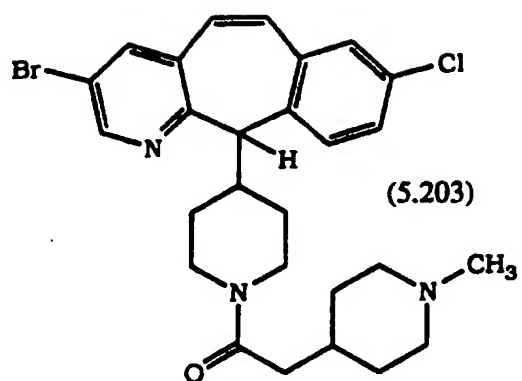
- 27 -

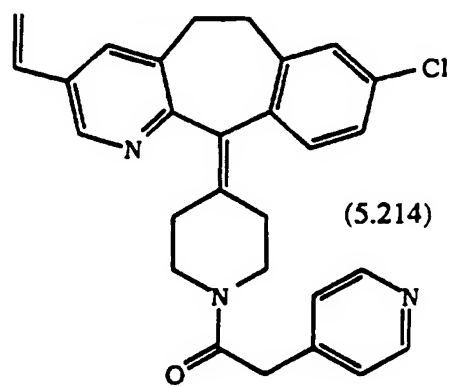
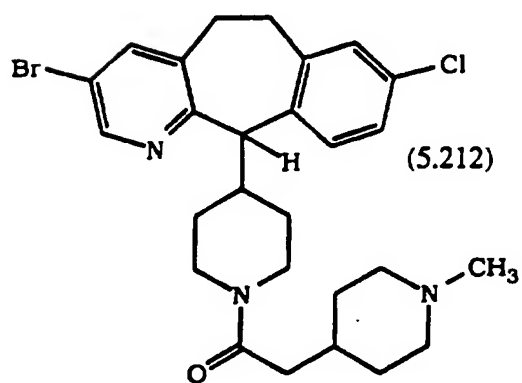
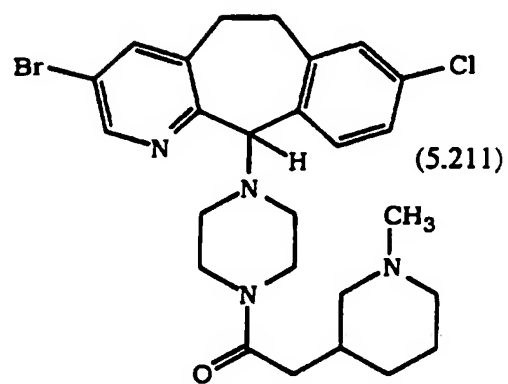
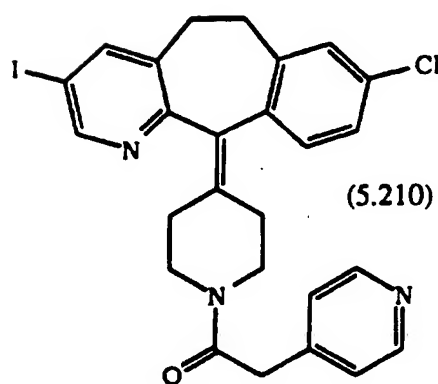
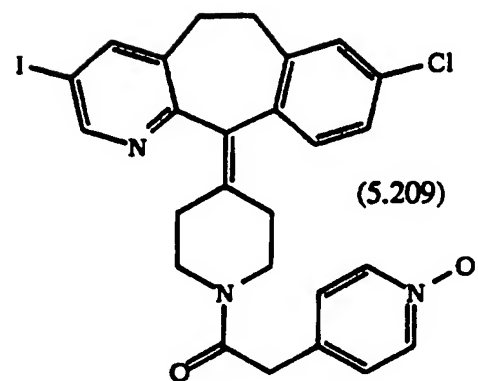
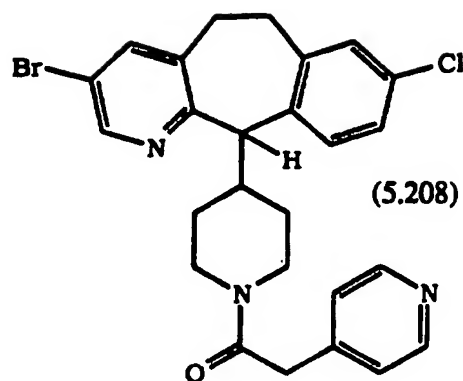


Preferably for the compounds of Formulas 5.3, 5.3a-5.3h, 5.3A, 5.3Aa-5.3Ah, and 5.3B, R^{25} represents phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, or 2-, 3- or 4-pyridyl N-oxide, and most preferably 4-pyridyl or 4-pyridyl N-oxide. More preferably, R^{48} represents H or methyl and still more preferably H.

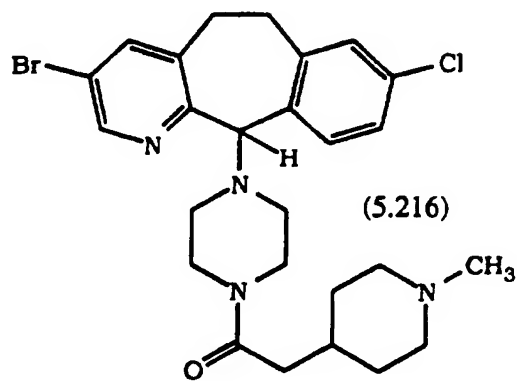
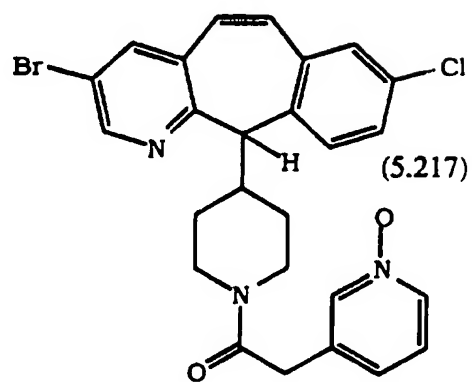
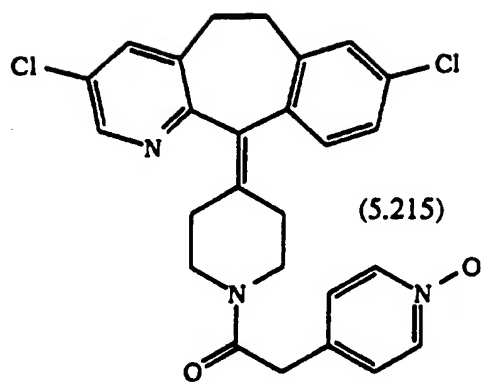
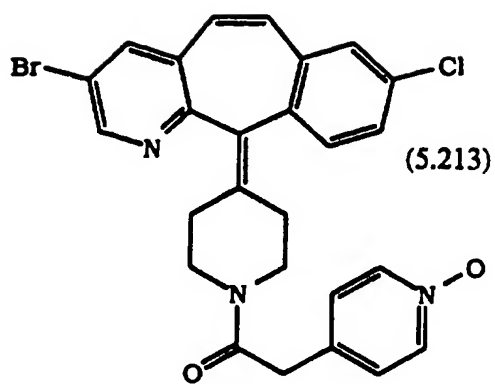
Representative compounds of the invention include:

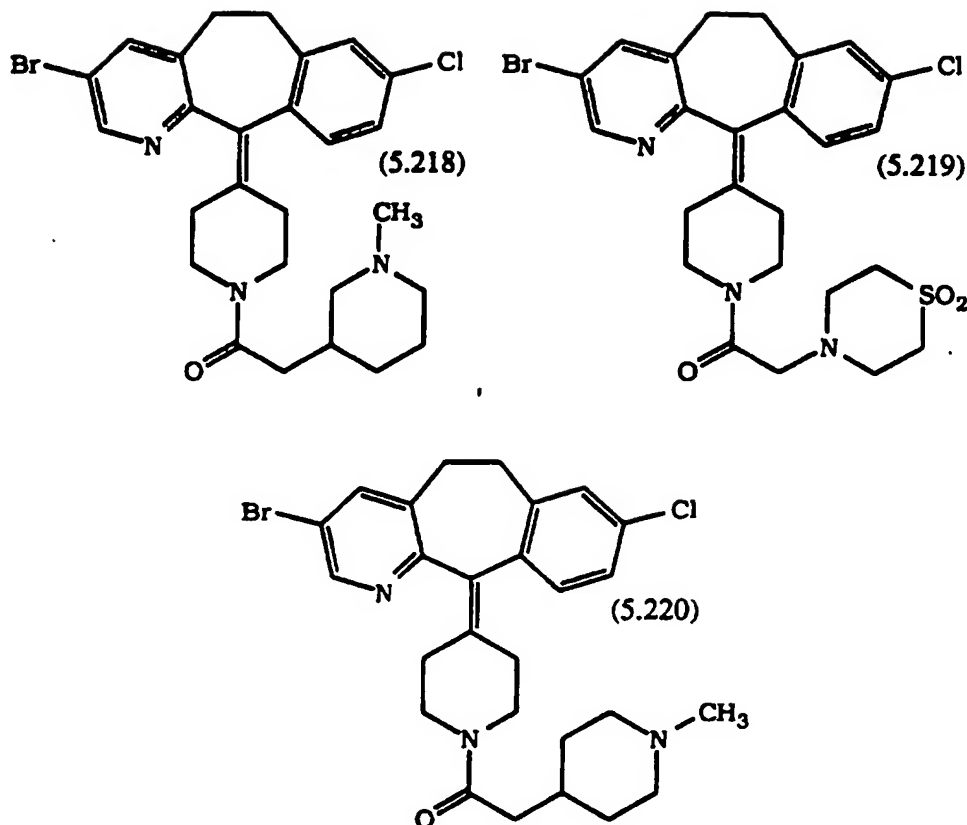






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5 Preferred compounds are the compounds of Examples: 426, 400-G, 400-C, 400-F, 400-E, 425-H, 401, 400-B, 400, 400-L, 425-U, 413, 400-J, 417-B, 438, 411-W, 425-O, 400-D, 400-K, 410-G and 400-H.

Lines drawn into the ring systems indicate that the indicated bond may be attached to any of the substitutable ring carbon atoms.

10 Certain compounds of the invention may exist in different isomeric (e.g., enantiomers and diastereoisomers) forms. The invention contemplates all such isomers both in pure form and in admixture, including racemic mixtures. Enol forms are also included.

Certain tricyclic compounds will be acidic in nature, e.g. those
 15 compounds which possess a carboxyl or phenolic hydroxyl group. These compounds may form pharmaceutically acceptable salts. Examples of such salts may include sodium, potassium, calcium, aluminum, gold and silver salts. Also contemplated are salts formed with pharmaceutically acceptable amines such as ammonia, alkyl amines, hydroxyalkylamines,
 20 N-methylglucamine and the like.

Certain basic tricyclic compounds also form pharmaceutically acceptable salts, e.g., acid addition salts. For example, the pyrido-

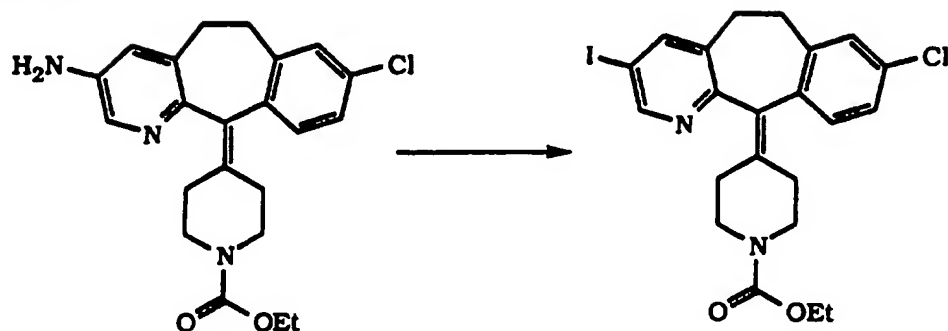
nitrogen atoms may form salts with strong acid, while compounds having basic substituents such as amino groups also form salts with weaker acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous NaOH, potassium carbonate, ammonia and sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the acid and base salts are otherwise equivalent to their respective free base forms for purposes of the invention.

All such acid and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

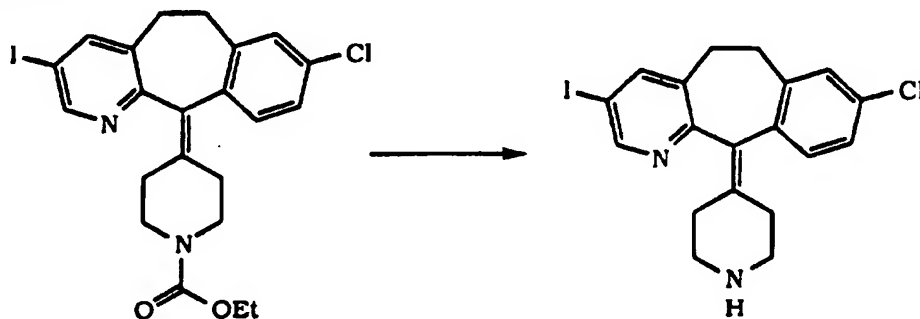
Compounds of the invention may be made by the methods described in the examples below, and by the methods described in WO 95/10516 published April 20, 1995--see, for example, the methods for preparing compounds of Formula 400.00.

On page 57 at lines 7 to 16 of WO 95/10516 a process is disclosed for introducing substituents at the C-3 position of pyridine Ring I of Formula 1.0 by nitrating a compound of Formula 415.00. The nitro group may then be reduced to the corresponding amine using the disclosed reagents or powdered Zn and either CuCl₂ or CuBr₂ in aqueous EtOH.

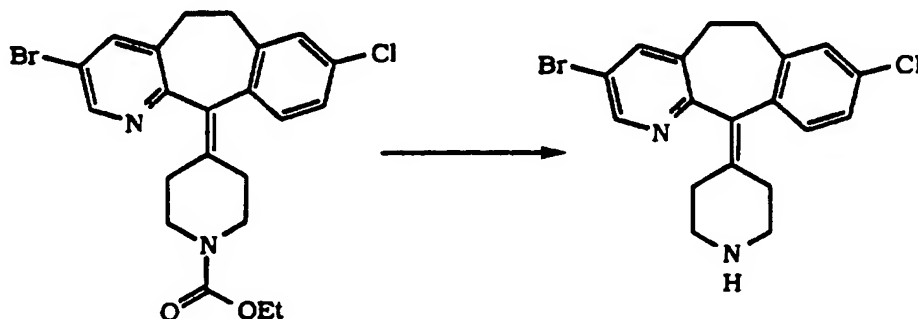
Compounds useful in this invention are exemplified by the following preparative examples, which should not be construed to limit the scope of the disclosure. Alternative mechanistic pathways and analogous structures within the scope of the invention may be apparent to those skilled in the art.

PREPARATIVE EXAMPLE 48**Step A:**

- Combine 6 g (15.11 mmol) of the title compound of Preparative Example 47B, of WO 95/10516, and benzene, and add 2.3 g (9.06 mmol) of iodine. Heat the mixture at reflux for 3 hours, cool, then dilute with 50 mL of CH₂Cl₂. Wash the organic phase with 5% NaHSO₃(aqueous) (3 x 80 mL), then with 1M NaOH (aqueous) (2x 80 mL), and dry over MgSO₄. Concentrate to a residue chromatograph (silica gel, 30% EtOAc/hexanes), to give 3.2 g (42% yield) of the product iodo compound. Mass Spec.: MH⁺ = 509

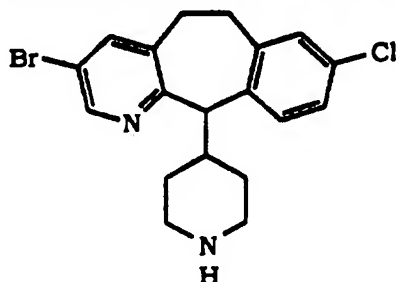
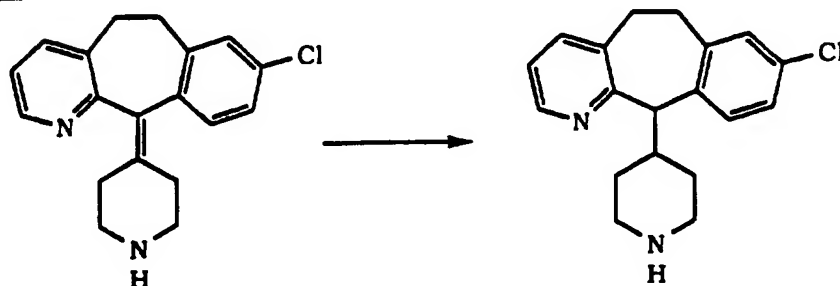
Step B:

- The product of Step A is hydrolyzed via substantially the same procedure as described in Example 358, Step A, of WO 95/10516, to give the iodoamine product in 89% yield.

PREPARATIVE EXAMPLE 49

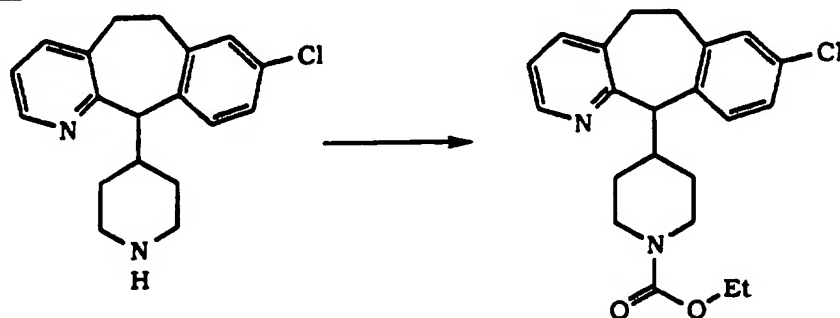
The product of Preparative Example 47, Step C, of WO 95/10516, (2.42 g) is hydrolyzed via substantially the same procedure as described in Example 358, Step A, of WO 95/10516, to give 1.39 g (69% yield) of the bromoamine product.

5

PREPARATIVE EXAMPLE 51A**Step A:**

Combine 82.0 g (0.26 mole) of the product of Preparative Example 1, Step G, of WO 95/10516, and 1 L of toluene, then add 20.06 g (0.53 mole) of LiAlH_4 and heat the reaction mixture at reflux overnight. Cool the mixture to room temperature and add ~1 L of Et_2O , followed by dropwise addition of saturated Na_2SO_4 (aqueous) until a precipitate forms. Filter and stir the filtrate over MgSO_4 for 30 minutes, then concentrate *in vacuo* to give the product compound in 83% yield. Mass Spec.: $\text{MH}^+ = 313$

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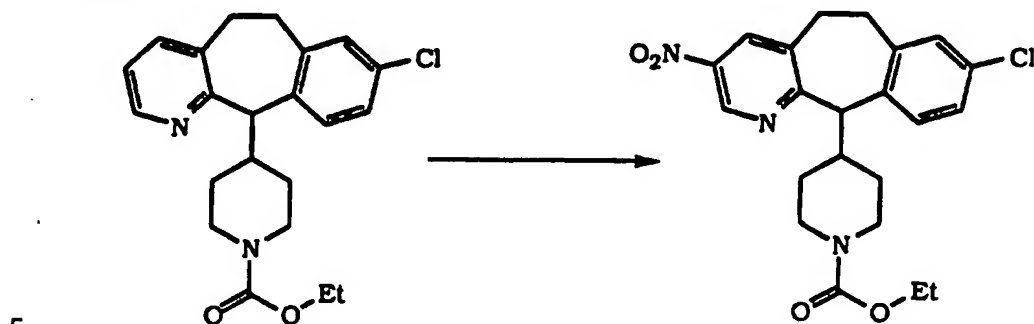
Step B:

Combine 24.32 g (74.9 mmol) of the Product from Step A, 500 mL of toluene, 83 mL of Et_3N and 65.9 mL of ethyl chloroformate and heat the mixture at reflux overnight. Cool to 25°C , pour into 200 mL of water and

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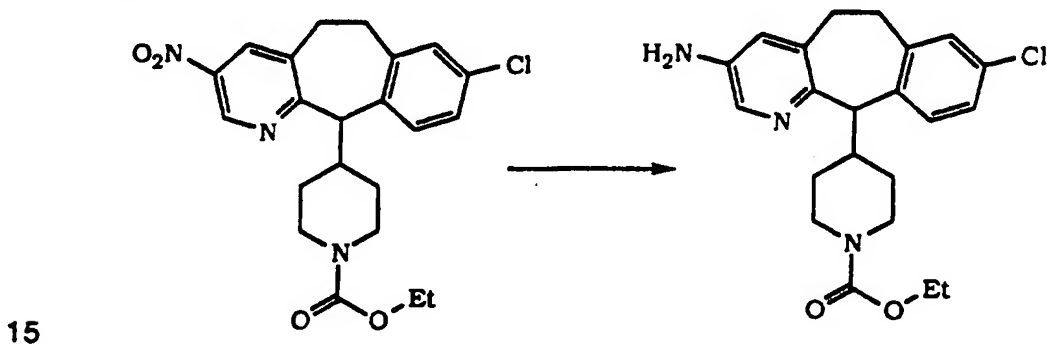
extract with EtOAc. Dry the extract over MgSO_4 , concentrate *in vacuo* to a residue and chromatograph (silica gel, 50% EtOAc/hexane) to give 15 g of the product compound. Mass Spec.: $\text{MH}^+ = 385$.

Step C:

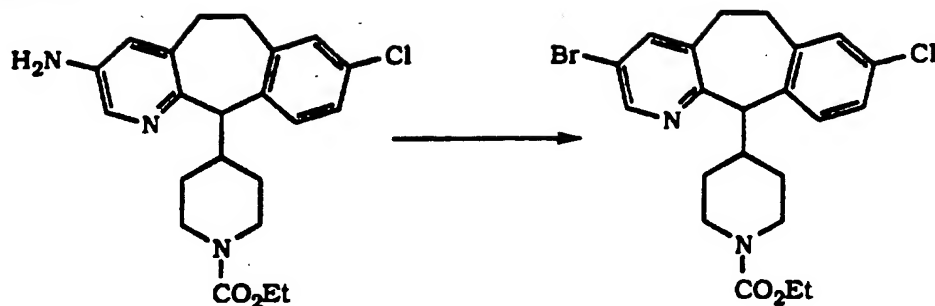


- Dissolve 3.2 g (10.51 mmol) of tetra-n-butylammonium nitrate in 25 mL of CH_2Cl_2 and add 2.2 g (10.51 mmol, 1.5 mL) of TFAA. Cool to 0°C and add the mixture (via cannula) to a solution of 3.68 g (9.56 mmol) of the product of Step B in 50 mL of CH_2Cl_2 at 0°C , then stir at 0°C for 3 hours.
- 10 Allow the mixture to warm to 25°C while stirring overnight, then extract with saturated NaHCO_3 (aqueous) and dry over MgSO_4 . Concentrate *in vacuo* to a residue and chromatograph (silica gel, 30% EtOAc/hexane) to give 1.2 g of the product compound. Mass Spec.: $\text{MH}^+ = 430$

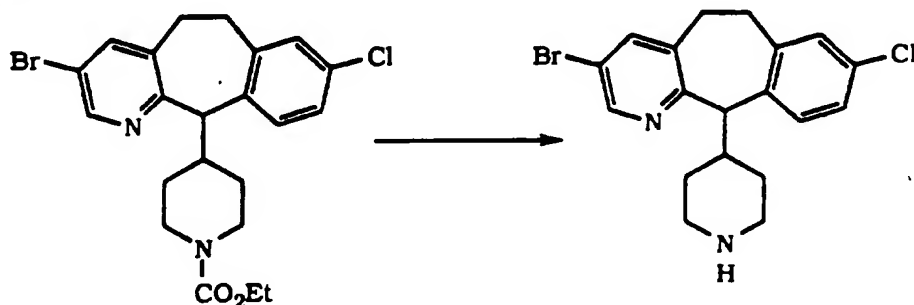
Step D:



- Combine 2.0 g (4.7 mmol) of the Product of Step C and 150 mL of 85% EtOH (aqueous), add 2.4 g (42 mmol) of Fe filings and 0.24 g (2.1 mmol) of CaCl_2 , and heat at reflux for 16 hours. Filter the hot mixture through a bed of celite®, wash the celite® with hot EtOH. Concentrate the
- 20 filtrate *in vacuo* to give a 100% yield of the product compound. Mass Spec.: $\text{MH}^+ = 400$.

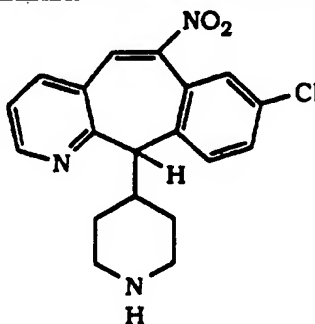
Step E:

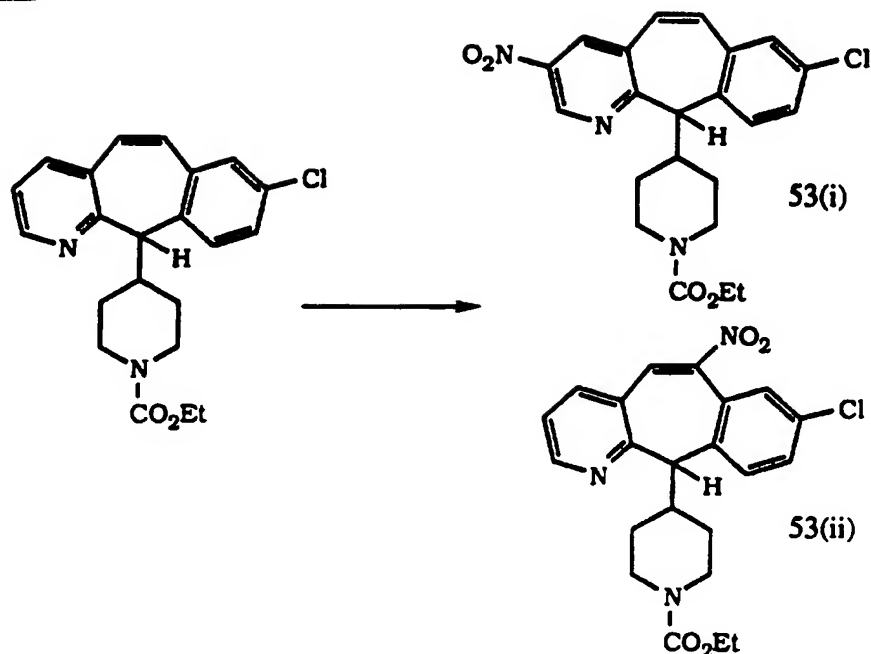
- Combine 2.0 g (5.2 mmol) of the Product of Step D and 20 mL of 48% HBr, cool the mixture to -5°C . Stir the mixture at -5°C for 15 minutes and slowly add a solution of 1.07 g (15.5 mmol) of NaNO_2 in 10 mL of water. Stir for 45 minutes, then quench with 50% NaOH (aqueous) to pH ~10. Extract with EtOAc, dry the combined extracts over MgSO_4 and concentrate *in vacuo* to give the product compound. Mass Spec.: $\text{MH}^+ = 465$

10 **Step F:**

- Hydrolyze 4.0 g of the Product of Step E via substantially the same process as described for Example 358, Step A, of WO 95/10516, to give 1.39 g of the product compound. Mass Spec.: $\text{MH}^+ = 392$

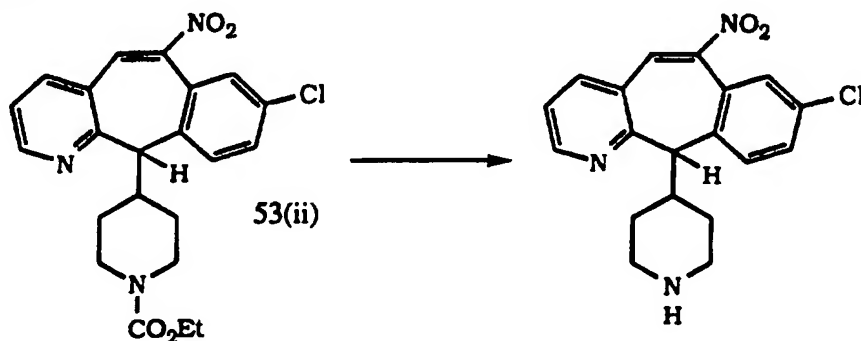
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PREPARATIVE EXAMPLE 53

Step A:

Combine 14.95 g (39 mmol) of the Product of Preparative Example 34A, of WO 95/10516, and 150 mL of CH_2Cl_2 , then add 13.07 g (42.9 mmol) of $(n\text{Bu})_4\text{NNO}_3$ and cool the mixture to 0°C . Slowly add (dropwise) a solution of 6.09 mL (42.9 mmol) of TFAA in 20 mL of CH_2Cl_2 over 1.5 hours. Keep the mixture at 0°C overnight, then wash successively with saturated NaHCO_3 (aqueous), water and brine. Dry the organic solution over Na_2SO_4 , concentrate *in vacuo* to a residue and chromatograph the residue (silica gel, EtOAc/hexane gradient) to give 4.32 g and 1.90 g of the two product compounds 53(i) and 53(ii), respectively.

Mass Spec.(53(i)): $\text{MH}^+ = 428.2$; Mass Spec. (53(ii)): $\text{MH}^+ = 428.3$

Step B:

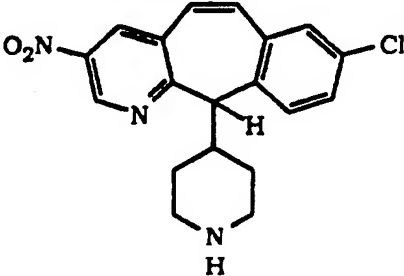
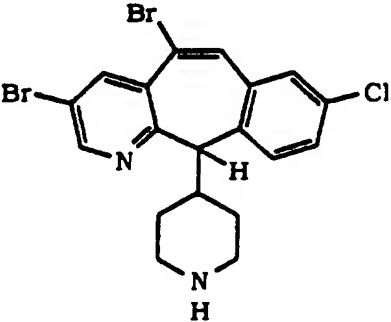
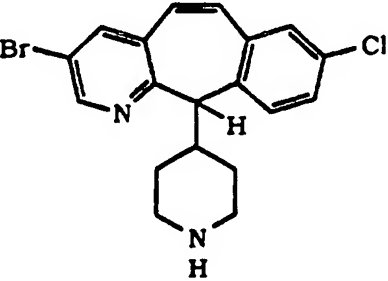
The compound 53(ii) from Step A (0.20 g) is hydrolyzed via substantially the same procedure as described for Example 358, Step A,

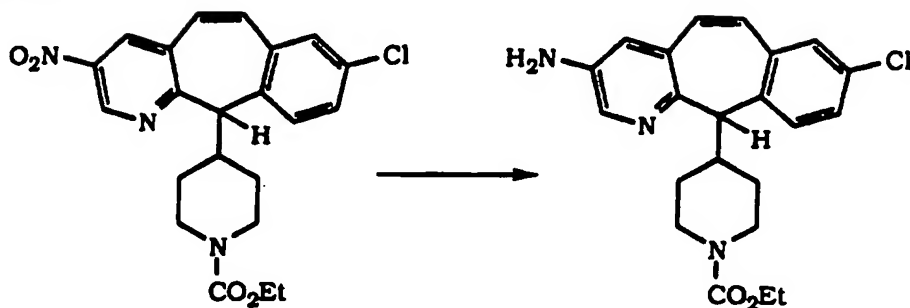
of WO 95/10516 (published April 20, 1995), to give 0.16 g of the product compound.

Using the starting compound indicated and substantially the same procedure as described in Preparative Example 53, Step B, the

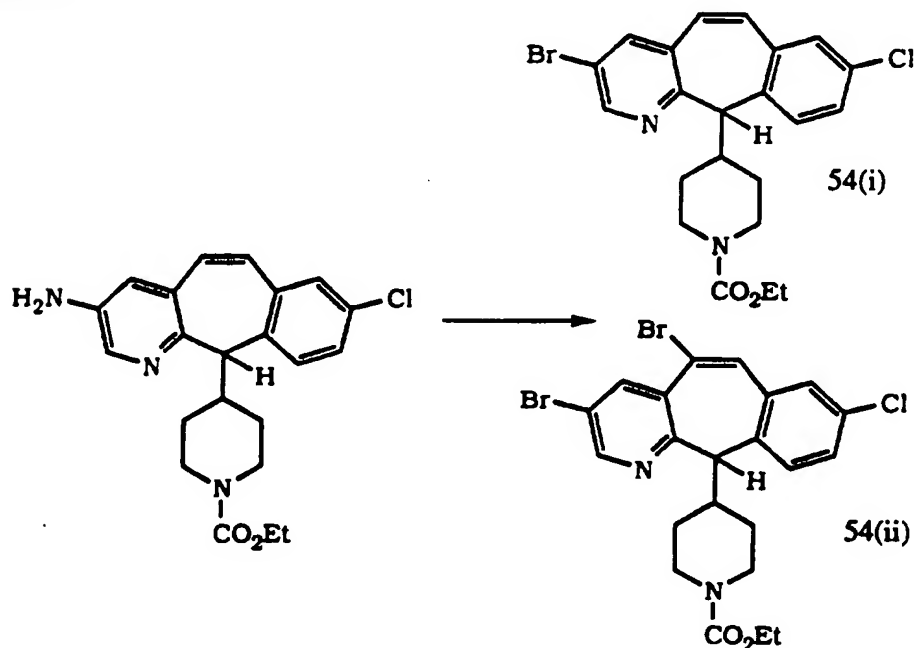
5 compounds in Table 1 are prepared:

TABLE 1

Starting Compound	Compound	Analytical Data
Preparative Example 53, Step A, compound 53(i)	 Preparative Example 53A	---
Preparative Example 54, Step B, compound 54(ii)	 Preparative Example 53B	Mass Spec.: MH ⁺ = 466.9
Preparative Example 54, Step B, compound 54(i)	 Preparative Example 53C	Mass Spec.: MH ⁺ = 466.9

PREPARATIVE EXAMPLE 54**Step A:**

- Combine 22.0 g (51.4 mmol) of the product 53(i) from Preparation 53, Step A, 150 mL of 85% EtOH (aqueous), 25.85 g (0.463 mole) of Fe powder and 2.42 g (21.8 mmol) of CaCl₂, and heat at reflux overnight. Add 12.4 g (0.222 mole) of Fe powder and 1.2 g (10.8 mmol) of CaCl₂ and heat at reflux for 2 hours. Add another 12.4 g (0.222 mole) of Fe powder and 1.2 g (10.8 mmol) of CaCl₂ and heat at reflux for 2 hours more. Filter the hot mixture through celite[®], wash the celite[®] with 50 mL of hot EtOH and concentrate the filtrate *in vacuo* to a residue. Add 100 mL of anhydrous EtOH, concentrate to a residue and chromatograph the residue (silica gel, MeOH/CH₂Cl₂ gradient) to give 16.47 g of the product compound.

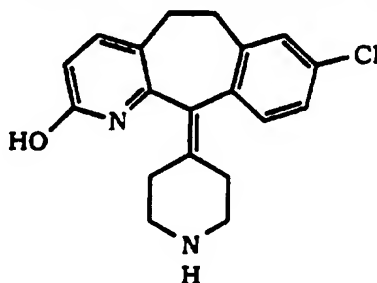
15 **Step B:**

Combine 16.47 g (41.4 mmol) of the product compound from Preparative Example 54, Step A, and 150 mL of 48% HBr (aqueous) and

cool to -3°C . Slowly add (dropwise) 18 mL of bromine, then slowly add (dropwise) a solution of 8.55 g (0.124 mole) of NaNO_2 in 85 mL of water. Stir for 45 minutes at -3° to 0°C , then adjust to $\text{pH} = 10$ by adding 50% NaOH (aqueous). Extract with EtOAc , wash the extracts with brine and dry the extracts over Na_2SO_4 . Concentrate to a residue and chromatograph (silica gel, EtOAc /hexane gradient) to give 10.6 g and 3.28 g of the two product compounds 54(i) and 54(ii), respectively.

Mass Spec. (54(i)): $\text{MH}^+ = 461.2$; Mass Spec. (54(ii)): $\text{MH}^+ = 539$

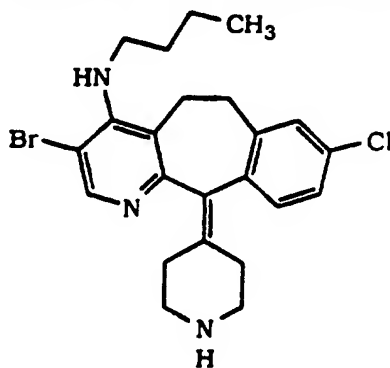
PREPARATIVE EXAMPLE 55



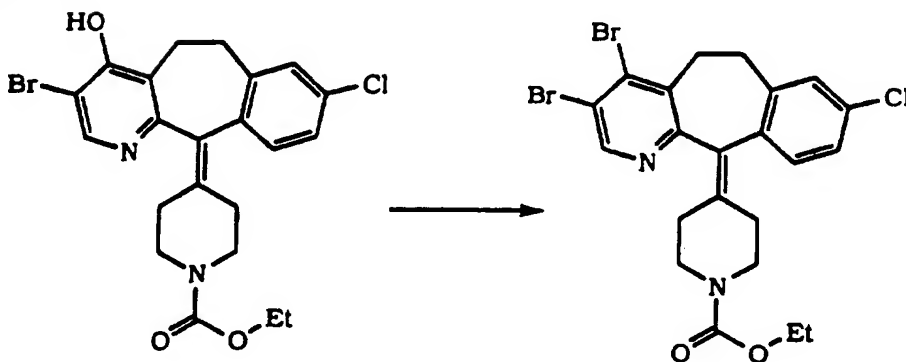
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The title compound is known and is prepared by the procedure described in Bioorg. & Med. Chem. Lett., 3, (No. 6) 1073-1078 (1993).

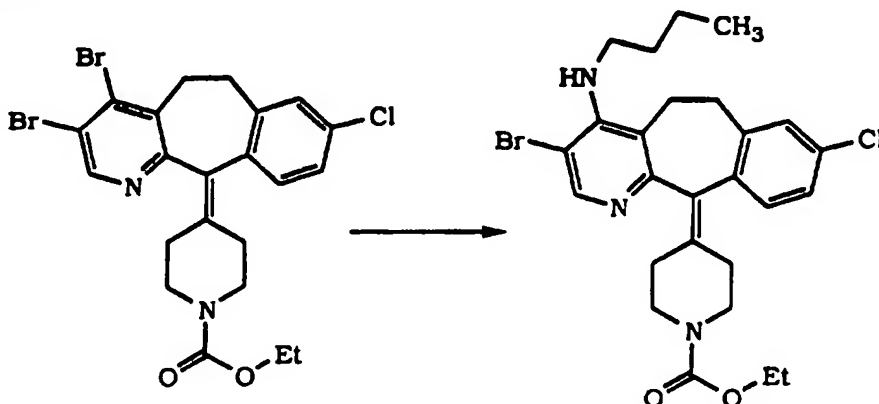
PREPARATIVE EXAMPLE 56



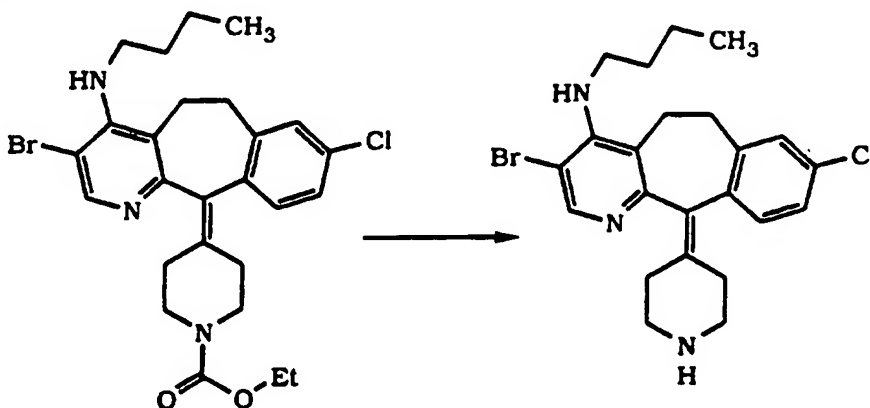
15 Step A:



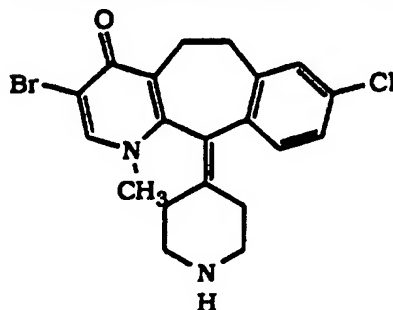
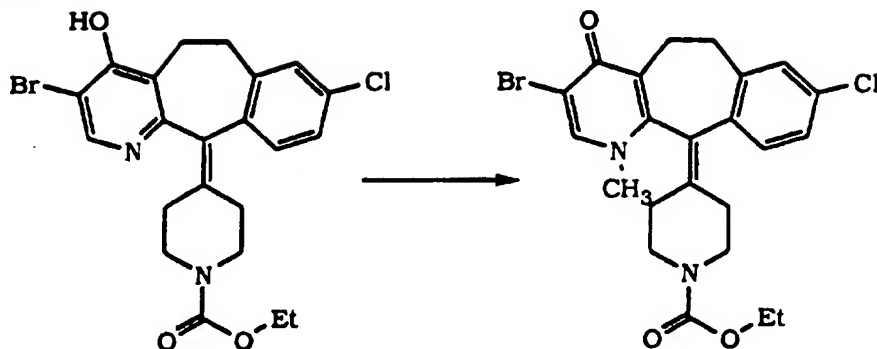
- Combine 2.04 g of the product of Preparative Example 44, of WO 95/10516 (published April 20, 1995), 1.3 mL of PBr_3 , 1.0 mL of Et_3N and 20 mL of CH_2Br_2 , and heat the mixture at reflux overnight. Cool the mixture, dilute with CH_2Cl_2 and wash with 1 N NaOH (aqueous). Dry over MgSO_4 and concentrate *in vacuo* to give 1.22 g (53% yield) of the product compound. Mass Spec.: $\text{MH}^+ = 541$

Step B:

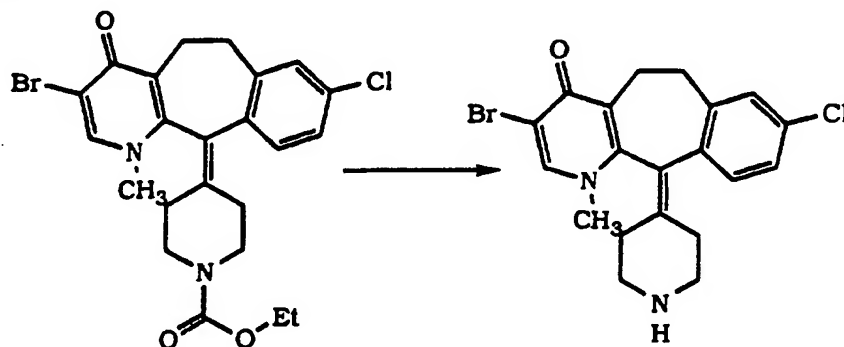
- Combine 0.3 g of the product compound from Preparative Example 56, Step A, and 8 mL of n-butylamine and stir at 120°C in a sealed tube for 48 hours. Concentrate *in vacuo* to a residue and purify by preparative plate chromatography (silica gel, 1.5-2.5% $\text{MeOH}/\text{CH}_2\text{Cl}_2$) to give 80 mg (27%) yield of the product compound. Mass Spec.: $\text{MH}^+ = 534$

Step C:

- Combine 66 mg of the product compound from Preparative Example 56, Step B, 4 mL of anhydrous EtOH , and 15 mL of concentrated HCl stir at reflux for 60 hours. Cool the reaction mixture to about 0°C and basify by adding KOH . Extract with CH_2Cl_2 , dry the extract over MgSO_4 , and concentrate *in vacuo* to give 46 mg (81% yield) of the product compound. Mass Spec.: $\text{MH}^+ = 462$

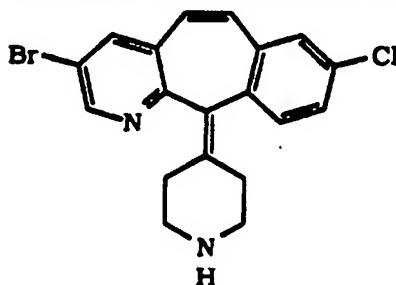
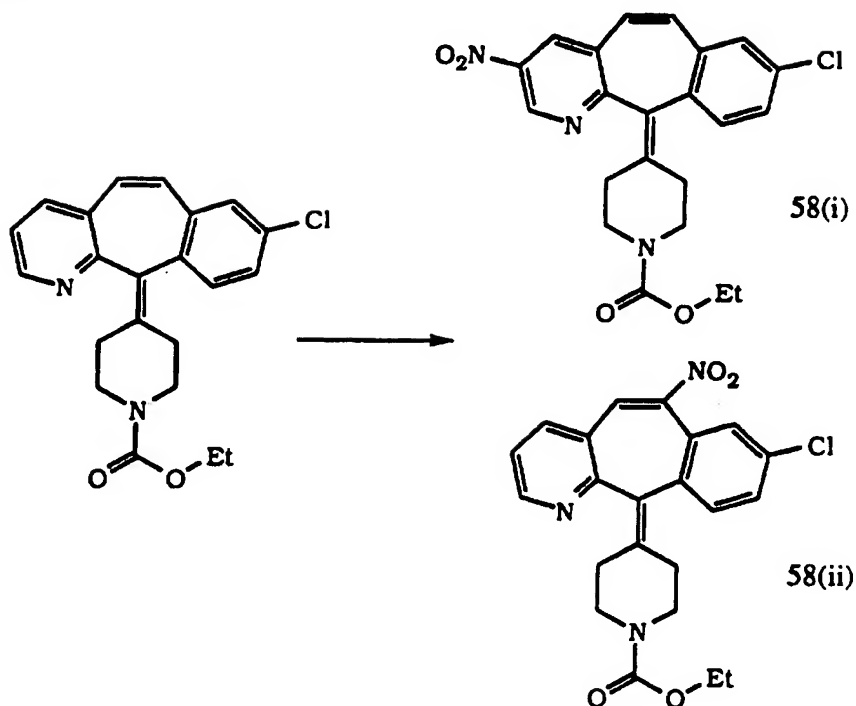
PREPARATIVE EXAMPLE 57**Step A:**

- 5 Combine 1.19 g of the product of Preparative Example 44, of WO 95/10516, 10 mL of anhydrous DMF, 0.2 g of NaH (60% in mineral oil) and 0.19 mL of methyl iodide, and stir at room temperature overnight. Concentrate *in vacuo* to a residue, dilute the residue with CH₂Cl₂, wash with saturated NaHCO₃ (aqueous), and dry over MgSO₄. Concentrate *in vacuo* to give 1.13 g (92% yield) of the product compound. Mass Spec.: MH⁺ = 493.
- 10

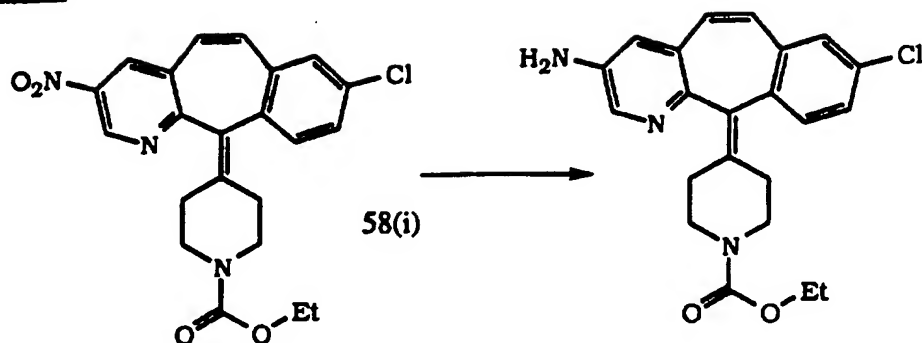
Step B:

- 15 Hydrolyze 1.13 g of the product of Step A via substantially the same procedure as described for Preparative Example 56, Step C, to give 0.61 g (63% yield) of the product compound.

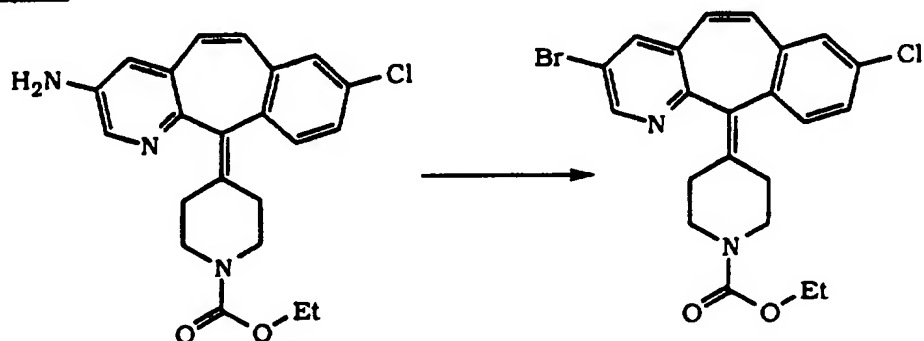
- 43 -

PREPARATIVE EXAMPLE 58**Step A:**

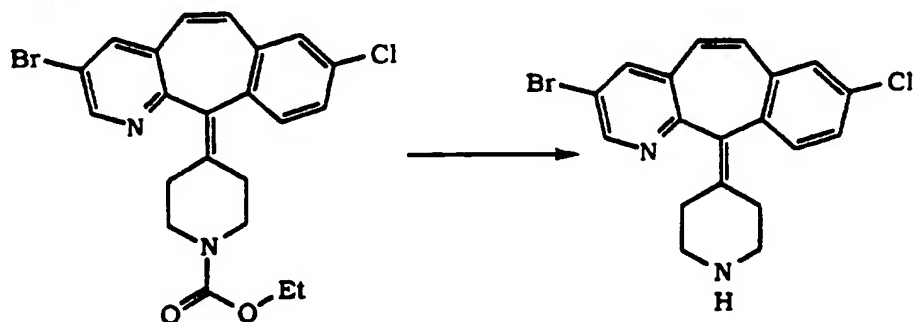
- 5 Combine 1.07 g (3.52 mmol) of tetrabutylammonium nitrate, 4 mL of anhydrous CH_2Cl_2 and 0.743 g (3.52 mmol) of TFAA, and add the resulting mixture to a solution of 1.22 g (3.20 mmol) of the title compound of Preparative Example 37, of WO 95/10516, in 8 mL of anhydrous CH_2Cl_2 at room temperature. Stir at room temperature overnight, then
- 10 wash with 20 mL of saturated NaHCO_3 (aqueous) and 20 mL of brine, and dry over MgSO_4 . Concentrate *in vacuo* and chromatograph the resulting residue (silica gel, EtOAc/hexane) to give 0.216 g of the product compound 58(i) and 0.27 g of the product compound 58(ii). Mass Spec. (58(i)): $\text{MH}^+ = 426$. m.p. (58(i)) $97.5^\circ - 99.2^\circ\text{C}$.

Step B:

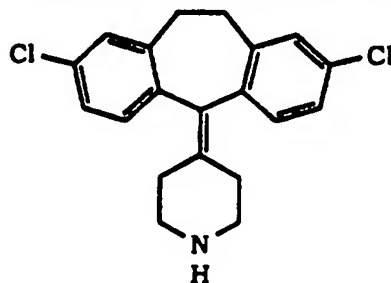
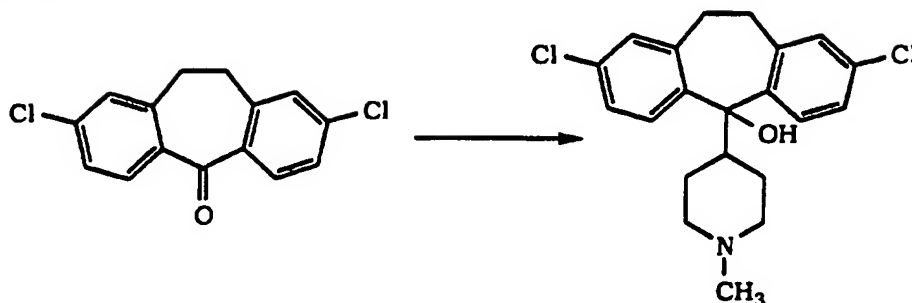
Reduce the product 58(i) from Step A via essentially the same procedure as described in Preparative Example 47, Step B, of WO 95/10516, to give the product compound. Mass Spec.: $MH^+ = 396$

Step C:

React the product from Step B with HBr and bromine via essentially the same procedure as described in Preparative Example 47, Step C, of WO 95/10516, to give the product compound. Mass Spec.: $MH^+ = 459$

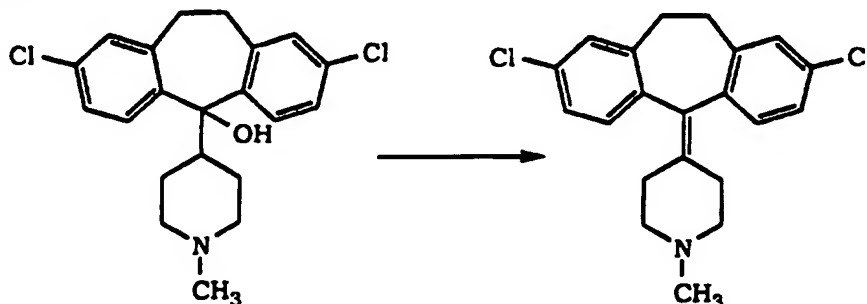
Step D:

Hydrolyze 0.83 g of the product from Step C via essentially the same procedure as described in Preparative Example 56, Step C, to give 0.56 g of the product compound. Mass Spec.: $MH^+ = 387$

PREPARATIVE EXAMPLE 59**Step A:**

- 5 Combine 7.3 g (26.4 mmol) of the starting ketone (see J. Med. Chem., 4238 (1992)) and 230 mL of THF and cool to 0°C. Add a solution of 32.2 mmol) of N-methyl-piperidine-4-magnesium bromide in 26 mL of THF and stir at 0°-5°C for 4 hours. Add 400 mL of EtOAc, wash with saturated NH₄Cl (aqueous), and dry over MgSO₄. Concentrate *in vacuo*
- 10 to a residue, add ~200 mL of CH₂Cl₂ and stir for 0.5 hours. Filter to collect the resulting solid and concentrate the filtrate to a volume of ~100 mL and let sit at 5 °C for 18 hours. Filter and combine the solids to obtain a total of 7 g (19.4 mmol) of the product compound. m.p.=153.7°-158 °C; Mass Spec.: (Cl) MH⁺ = 376

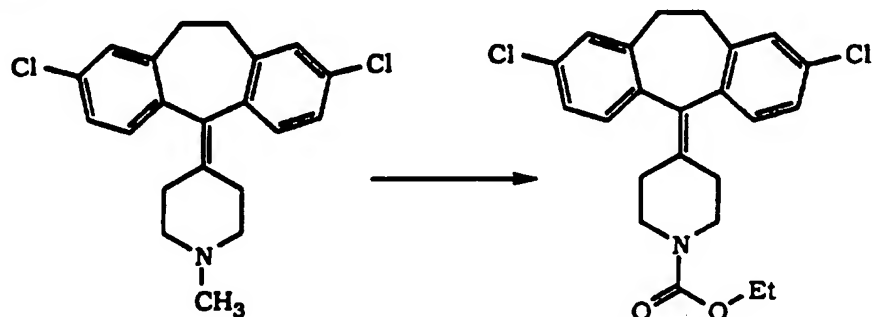
15 **Step B:**



Combine 5 g of the product from Step A and 30 mL of TFA at ambient temperature and stir for 1 hour. Concentrate *in vacuo* to a residue, dissolve the residue in CH₂Cl₂ and wash with a saturated

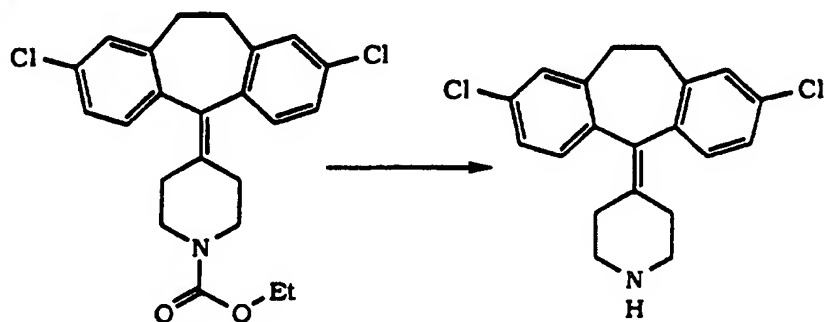
NaHCO_3 (aqueous). Concentrate *in vacuo* to give 4.64 g of the product compound. m.p.= 136.7°-138°C; Mass Spec.: (FAB) $\text{MH}^+ = 358.1$

Step C:

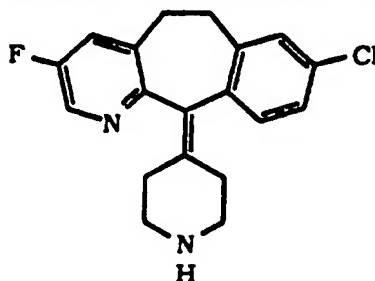
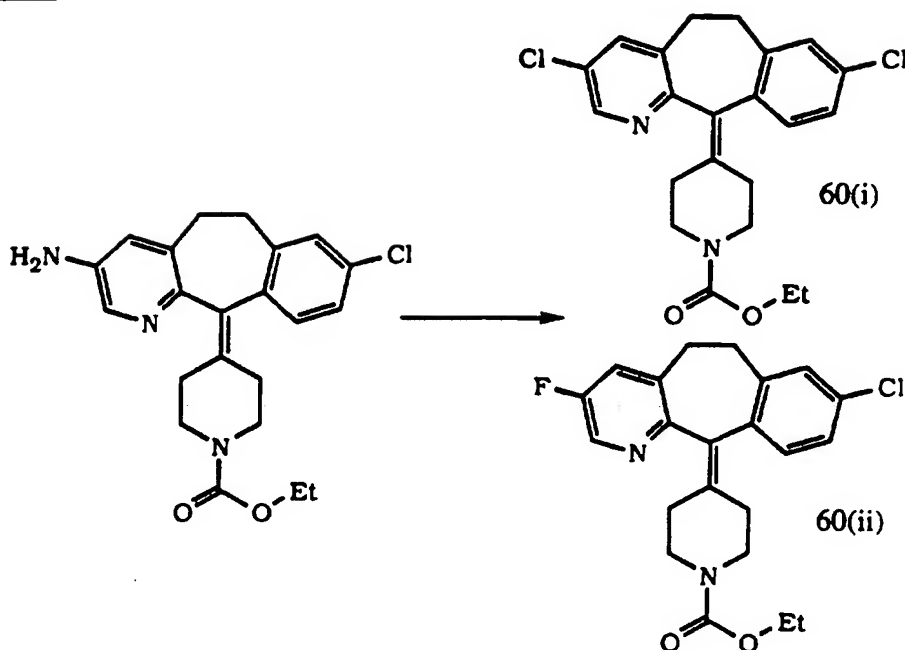


- 5 Combine 0.6 g (1.75 mmol) of the product of Step B and 25 mL of toluene, add 0.73 mL (5.27 mmol) of Et_3N and 1.34 mL (14 mmol) of ClCO_2Et , and heat to 80°C for 2 hours. Add 0.7 mL more of ClCO_2Et , heat for 1 more hour, then cool to 25 °C and concentrate *in vacuo* to a residue. Dissolve the residue in EtOAc and wash with 1N NaOH (aqueous)
- 10 followed by brine. Dry over MgSO_4 , concentrate *in vacuo* to a residue and chromatograph (silica gel, 10% EtOAc/hexanes) to give 0.55 g of the product compound. Mass Spec.: (FAB) $\text{MH}^+ = 416.2$

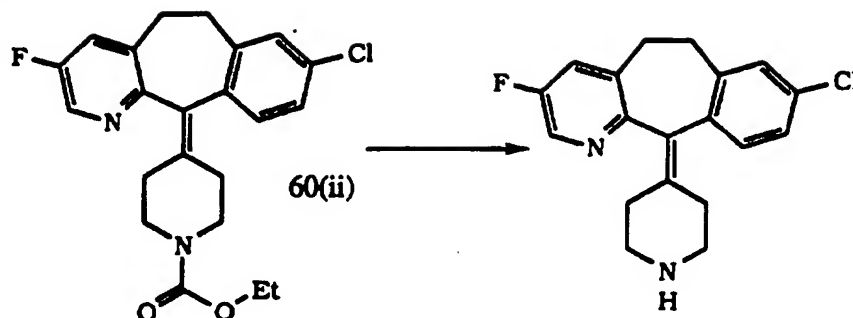
Step D:



- 15 Dissolve 5 g (12.5 mmol) of the product of Step C in 30% HBr in HOAc and heat at 40°C for 24 hours, then cautiously add the mixture to cold 25 % NaOH (aqueous). Extract with CH_2Cl_2 (3 X 100 mL), concentrate the extracts to a residue and chromatograph (silica gel, 5% to 30 % MeOH/ CH_2Cl_2) to give 2.18 g of the product compound.
- 20 m.p.= 159.5°-160.8°C; Mass Spec.: (FAB) $\text{MH}^+ = 344.1$

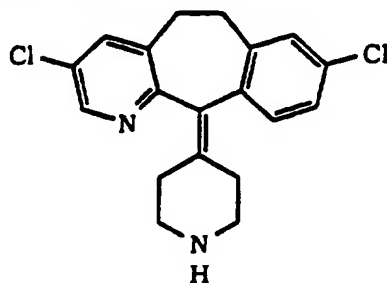
PREPARATIVE EXAMPLE 60Step A:

- 5 Combine 16.25 g (40.83 mmol) of the product of Preparative Example 47, Step B, of WO 95/10516, and a slurry of 7.14 g (61.11 mmol) of NOBF_4 in 100 mL of CH_2Cl_2 and stir the mixture for 3 hours. Add 100 mL of o-dichlorobenzene and heat for 5 hours, distilling the CH_2Cl_2 from the mixture. Concentrate *in vacuo* to a residue, add 200 mL of CH_2Cl_2 and
- 10 wash with water (2 X 200 mL). Dry over MgSO_4 , concentrate *in vacuo* to a residue, and chromatograph (silica gel, 20% EtOAc/hexane) to give 4.1 g of product compound 60(i) and 4.01 g of Product compound 60(ii). Mass Spec. (60 (i)): $\text{MH}^+ = 418$. Mass Spec. (60 (ii)): $\text{MH}^+ = 401$

Step B:

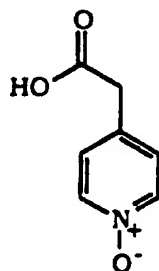
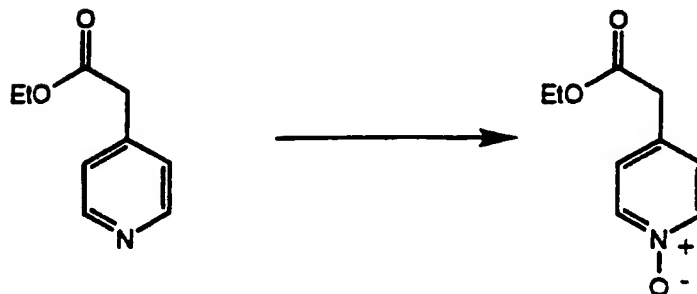
Hydrolyze 3.4 g of the product 60 (ii) from Step A via essentially the same process as described for Example 358, Step A, of WO 95/10516, to give 3.01 g of product compound. Mass Spec.: $MH^+ = 329$

Using compound 60(i) from Preparative Example 60, Step A, and following substantially the same procedure as described in Preparative Example 60, Step B, the compound:

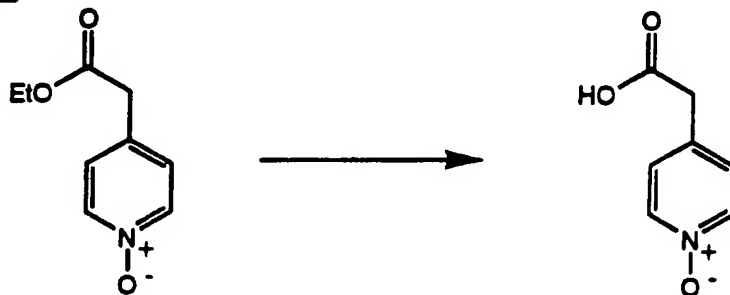


(Preparative Example 60A)

was prepared. Mass Spec.: $MH^+ = 346$.

PREPARATIVE EXAMPLE 61Step A:

Combine 10 g (60.5 mmol) of ethyl 4-pyridylacetate and 120 mL of dry CH_2Cl_2 at -20°C , add 10.45 g (60.5 mmol) of MCPBA and stir at -20°C for 1 hour and then at 25°C for 67 hours. Add an additional 3.48 g (20.2 mmol) of MCPBA and stir at 25°C for 24 hours. Dilute with CH_2Cl_2 and wash with saturated NaHCO_3 (aqueous) and then water. Dry over MgSO_4 , concentrate *in vacuo* to a residue, and chromatograph (silica gel, 2%-5.5% (10% NH_4OH in MeOH)/ CH_2Cl_2) to give 8.12 g of the product compound. Mass Spec.: $\text{MH}^+ = 182.15$

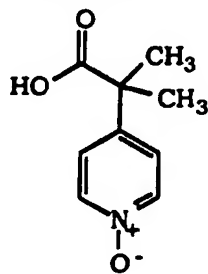
Step B:

10

Combine 3.5 g (19.3 mmol) of the product of Step A, 17.5 mL of EtOH and 96.6 mL of 10% NaOH (aqueous) and heat the mixture at 67°C for 2 hours. Add 2 N HCl (aqueous) to adjust to $\text{pH} = 2.37$ and concentrate *in vacuo* to a residue. Add 200 mL of dry EtOH , filter through celite® and wash the filter cake with dry EtOH (2X50 ml). Concentrate the combined filtrates *in vacuo* to give 2.43 g of the title compound.

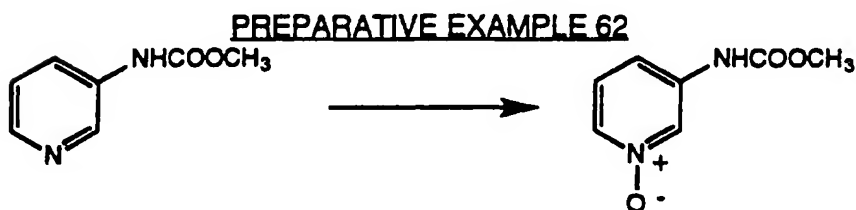
15

Using the product of Preparative Example 26, of WO 95/10516, and substantially the same procedure as described for Preparative Example 61, Steps A and B, the following compound was prepared:



(61A)

20



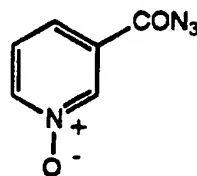
Combine 10 g (65.7 mmol) of 3-methoxycarbonylaminopyridine and 150 mL of CH_2Cl_2 , cool to 0°C and slowly add (dropwise) a solution

of 13.61 g (78.84 mmol) of MCPBA in 120 mL of CH_2Cl_2 at 0°C over a period of 1 hour. Stir the mixture at 25°C for 5 days, then wash with saturated NaHCO_3 (aqueous), then water and dry over MgSO_4 . Concentrate *in vacuo* to a residue and chromatograph (silica gel, 2%-5% (10% NH_4OH in MeOH)/ CH_2Cl_2) to give the product compound. Mass Spec.: $\text{MH}^+ = 169$

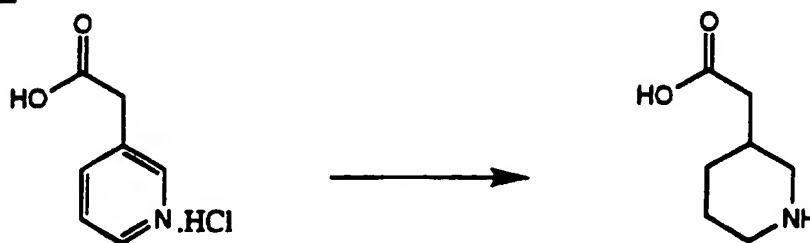
PREPARATIVE EXAMPLE 63

Combine 5 g (36.0 mmol) of isonicotinic acid 1-N-oxide and 150 mL of anhydrous DMF, add 5.5 mL (39.6 mmol) of Et_3N and stir at 0°C for 0.5 hours. Slowly add (dropwise) 8.5 mL (39.6 mmol) of diphenylphosphoryl azide at 0°C over 10 minutes, stir at 0°C for 1 hour and then at 25°C for 24 hours (as generally described in Pavia, *et al.*, Journal of Medicinal Chemistry, **33**, 854-861 (1990). Concentrate *in vacuo* to a residue and chromatograph (silica gel, 0.5%-1% $\text{MeOH}/\text{CH}_2\text{Cl}_2$) to give 5.9 g of the product compound.

Using nicotinic acid 1-N-oxide and substantially the same procedure as described for Preparative Example 63 the following compound was prepared:



(63A)

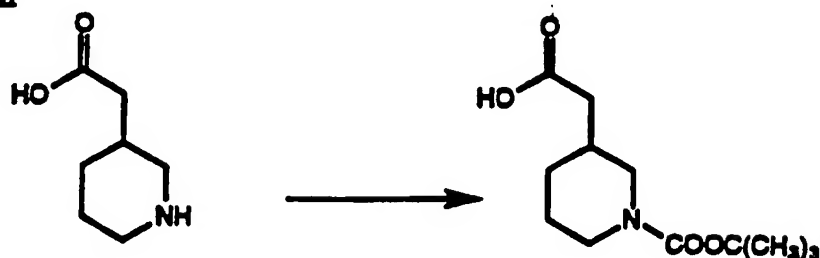
PREPARATIVE EXAMPLE 64**Step A:**

Hydrogenate 25 g (144 mmol) of 3-pyridylacetic acid hydrochloride for 144 hours using the procedure described in Preparative Example 15,

of WO 95/10516, to give 20 g of the product compound. Mass Spec.:

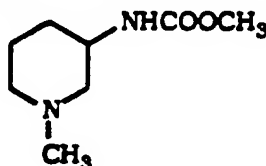
$MH^+ = 144$.

Step B:



- 5 React 12 g (83.8 mmol) of the product of Step B for 148 hours using the procedure described in Preparative Example 13, Step B, of WO 95/10516, to give 17.5 g of the product compound. Mass Spec.: $MH^+ = 244.25$

PREPARATIVE EXAMPLE 65

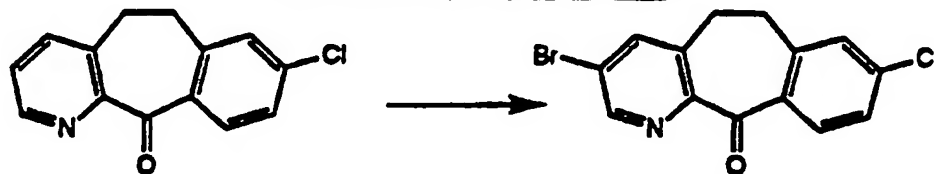


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- Combine 25 g (164.4 mmol) of methyl 3-pyridylcarbamate and 163.3 mL of 1N HCl (aqueous), stir until all of the solid dissolves, then hydrogenate over 10% Pd/C at 25°C at 55 psi for 220 hours. Filter, wash the solids with water and treat the combined filtrates with 150 mL of BioRad AG1X8 ion exchange resin (OH⁻). Filter, wash the resin with water and concentrate the filtrate to a volume of 100 mL. Add 16.43 mL (197.3 mmol) of 37% formalin and hydrogenate over 10% Pd/C at 25°C at 55 psi for 89 hours. Filter, wash the solids with water and concentrate *in vacuo* to give 24.3 g of the title compound. Mass Spec.: $MH^+ = 173.2$

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PREPARATIVE EXAMPLE 66



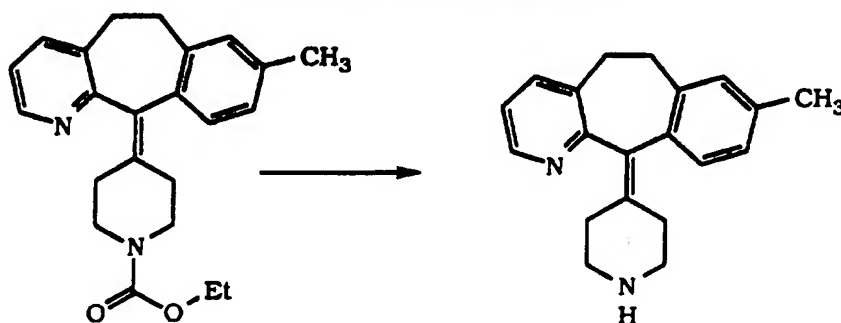
- Cool 50.0 g (20.5 mmol) of 8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one to 0°C, slowly add 75 mL (93.69 mmol) of sulfur monochloride over 20 minutes, then slowly add 25 mL (48.59 mmol) of Br₂ over 15. Heat at 95°C for 20 hour, add 12.5 mL (24.3 mmol) of Br₂ and heat for a another 24 hours. Cool the mixture, and slowly add to a mixture of CH₂Cl₂ and 1N NaOH (aqueous) at 0°C. Wash

25

the organic phase with water, dry over MgSO_4 and concentrate *in vacuo* to a residue. Chromatograph the residue (silica gel, 500 mL CH_2Cl_2 then 0.2%-5% (10% NH_4OH in MeOH)/ CH_2Cl_2), then chromatograph again (silica gel, 3%-8.5% EtOAc /hexane) to give 8.66 g of the product

5 compound. Mass Spec.: $\text{MH}^+ = 322$

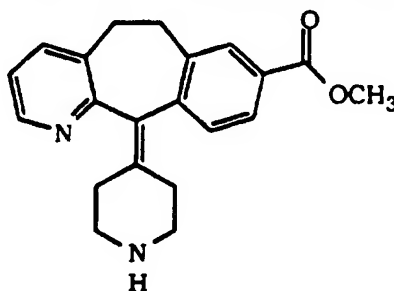
PREPARATIVE EXAMPLE 67



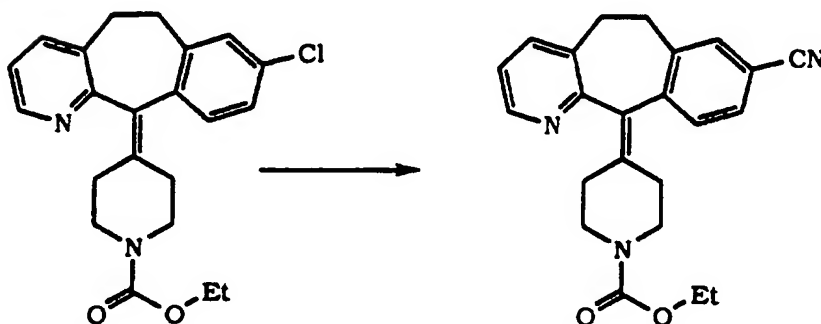
Dissolve 0.16 g (0.46 mmol) of 4-(8-methyl-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-ethoxycarbonylpiperidine, in 2 mL EtOH and add 4 mL of 12 N HCl . Heat the solution for 10 3 hours at 85°C , then cool to 25°C . Adjust to $\text{pH} = 10$ with 50% NaOH (aqueous) and extract several times with 50 mL of EtOAc . Combine the organic layers, dry them over MgSO_4 , and concentrate *in vacuo* to give the product compound.

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PREPARATIVE EXAMPLE 68

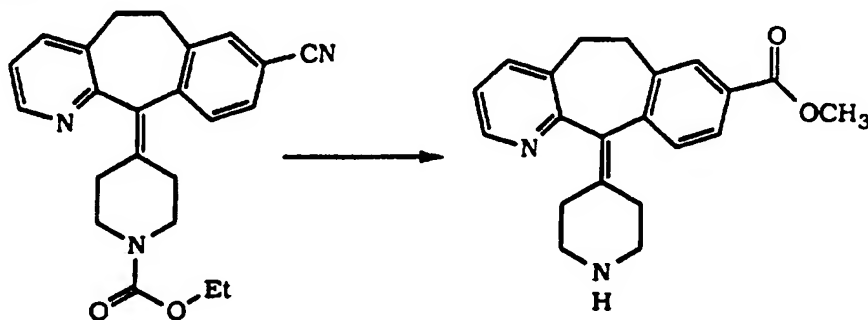


Step A:

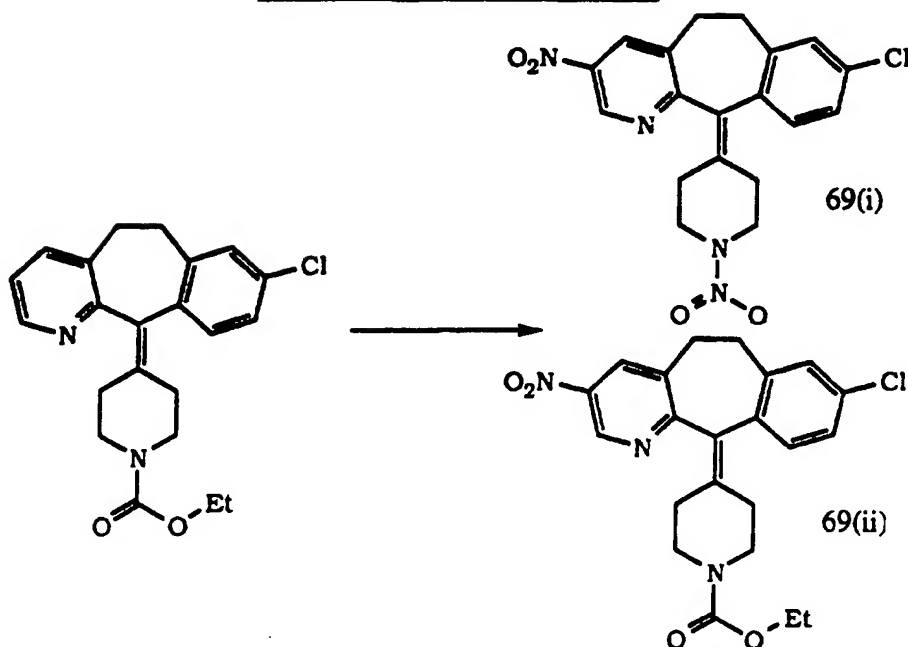


5 Dissolve 2 g (5.22 mmol) of the title compound of Preparative Example 1F, of WO 95/10516, in 2.6 mL of dry N-methylpyrrolidinone. Add 0.87 g (9.4 mmol) of CuCN and 0.139 g (0.93 mmol) of sodium iodide. Heat the mixture at 200°C under nitrogen for 20 hours, cool to 25°C and repeatedly grind and mix with five 50 mL portions of CH₂Cl₂ and 7 M NH₄OH (aqueous). Wash the organic layer with 7 M NH₄OH until the organic layer is no longer blue or green. Dry the combined organic layers over MgSO₄ and concentrate *in vacuo* to a residue. Chromatograph (silica gel 70% EtOAc/hexane), then recrystallize from EtOAc/hexane to give the product compound. m.p. = 152.4°-153.5°C; Mass Spec.: MH⁺ = 374

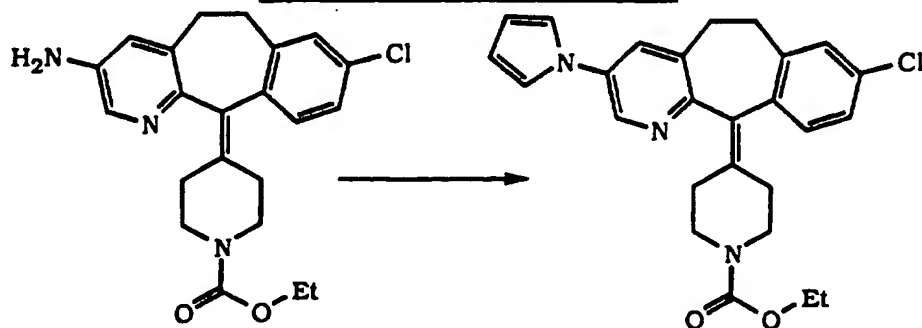
Step B:



15 Dissolve 4.08 g (10.93 mmol) of the product of Step A in 12 M HCl and heat at 85°C for 18 hours. Concentrate *in vacuo* to a residue. Dissolve the residue in 175 mL of MeOH, saturate with HCl gas, and heat at reflux for 18 hours. Concentrate *in vacuo* to give the product compound as its HCl salt. Mass Spec.: MH⁺ = 335

PREPARATIVE EXAMPLE 69

- Combine 75 g (0.196 mole) of the Product of Example 1, Step F, of WO 95/10516, and 300 mL of CH_2Cl_2 at 0°C , and slowly add (dropwise) a solution of 72 g (0.236 mole) of tetrabutylammonium nitrate and 35 mL (0.247 mole) of TFAA in 500 mL of CH_2Cl_2 . Stir at 25°C overnight, slowly add (dropwise) 1 L of saturated NaHCO_3 (aqueous). Separate the layers, wash the organic phase with brine and dry over MgSO_4 . Concentrate *in vacuo* to a residue, chromatograph twice (1 kg silica gel, gradient of EtOAc/ CH_2Cl_2) to give 8.63 g of product compound 69(i), and 34 g of product compound (ii). Recrystallize compound 69(i) from CH_2Cl_2 /hexane to give the purified product compound 69(i). m.p. = $186^\circ\text{--}187^\circ\text{C}$; Mass Spec.: (FAB) $\text{MH}^+ = 401$

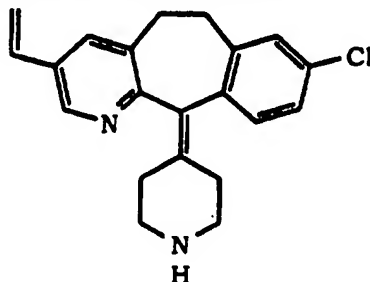
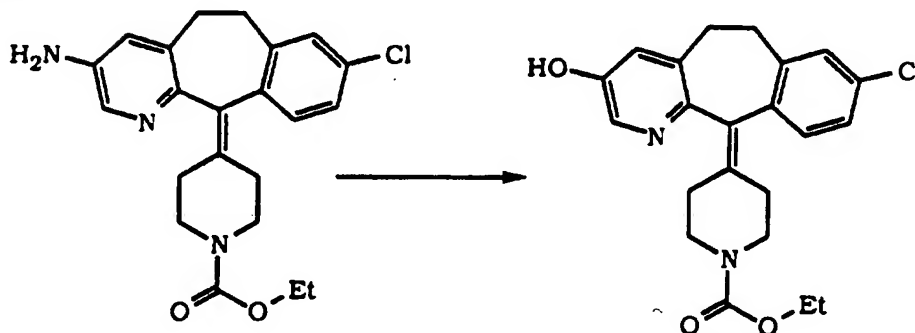
PREPARATIVE EXAMPLE 69A

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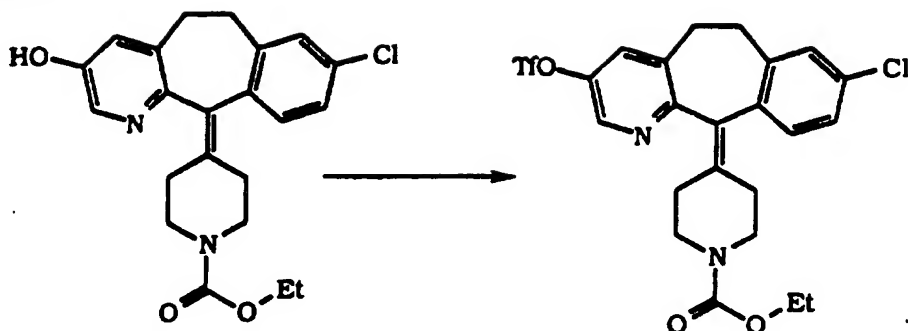
Combine 0.4 g (1 mmol) of the Product of Example 47, Step B, of WO 95/10516 (published April 20, 1995), and 0.2 mL (1.2 mmoles) of 2, 5-diethoxytetrahydrofuran in 3 mL of glacial HOAc, and heat at reflux for 1.5

hours. Cool the mixture, wash with saturated NaHCO_3 (aqueous), then with brine, dry over MgSO_4 , and concentrate *in vacuo* to a residue. Chromatograph (silica gel, 5%-15% $\text{EtOAc}/\text{CH}_2\text{Cl}_2$) to give 0.34 g of the product compound. Mass Spec.: (FAB) $\text{MH}^+ = 448$

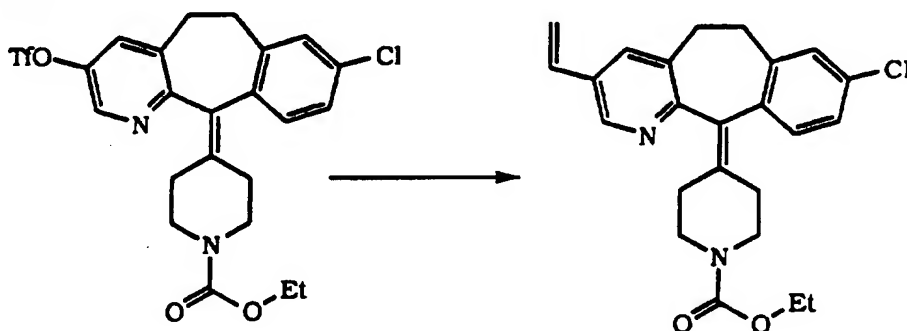
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PREPARATIVE EXAMPLE 70Step A:

- Combine 13.8 g (34.7 mmol) of the Product of Example 47, Step B, of WO 95/10516, and 90 mL of water at 0°C , add a solution of 6.9 mL of concentrated H_2SO_4 in 45 mL of water and stir the mixture. Slowly add (dropwise) a solution of 2.55 g (40 mmol) of NaNO_2 in 75 mL of water and stir at $0^\circ\text{-}5^\circ\text{C}$ for 0.5 hours. Add a boiling solution of 35.1 g CuSO_4 in 135 mL of water and heat at 100°C for 15 min. Cool the mixture, extract with CH_2Cl_2 (2 X 200 mL), wash the extracts with brine, dry over MgSO_4 , and concentrate *in vacuo* to a residue. Chromatograph (silica gel, 1.5%-10% $\text{MeOH}/\text{CH}_2\text{Cl}_2$) to give 11.36 g of the product compound.

Step B:

Combine 11.36 g (28.5 mmol) of the Product of Step A and 12.4 g (34.7 mmol) of N-phenyltriflimide in 120 mL of dry CH_2Cl_2 at 0°C , add 4.6 mL (33 mmol) of Et_3N and stir at 25°C overnight. Concentrate *in vacuo* to a residue and chromatograph (silica gel, 2%-5% $\text{EtOAc}/\text{CH}_2\text{Cl}_2$) to give 10.95 g of the product compound. Recrystallize from hot MeOH. m.p. = $154.5^\circ\text{--}156^\circ\text{C}$; Mass Spec.: (FAB) $\text{MH}^+ = 531$

Step C:

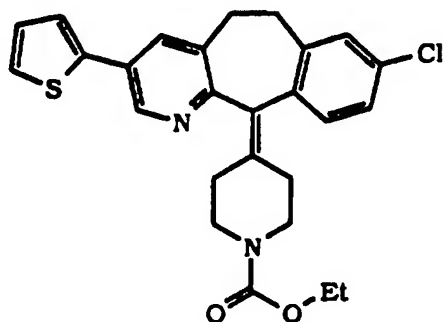
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Combine 12.2 g (23 mmol) of the Product of Step B and 85 mL of 1-methyl-2-pyrrolidinone at 25°C , then add 2.84 g LiCl , 0.212 g of tris-furylphosphine and 0.585 g of dipalladiumtribenzylideneacetone and stir for 15 min. Slowly add (dropwise) 7.5 mL (25.77 mmol) of tributylvinyltin and stir at 25°C for 2.5 hours. Dilute with 500 mL of water at 0°C and extract with 6700 mL of EtOAc . Filter the organic phase through celite®, wash the celite with EtOAc , then wash the filtrate twice with 30% NaF (aqueous). Filter the organic solution, wash with brine and dry over MgSO_4 . Concentrate *in vacuo* to a residue and chromatograph (silica gel, 15%-40% $\text{EtOAc}/\text{hexane}$) to give 8.58 g of the product compound. Mass Spec.: (FAB) $\text{MH}^+ = 409$

20

Using 2-(tributylstannyl)thiophene and the compound of Preparative Example 70, Step B, and following substantially the same

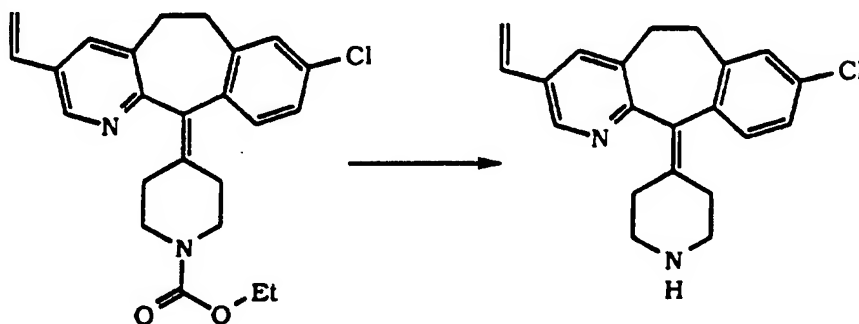
procedure as described for Preparative Example 70, Step C, the compound:



(Preparative Example 70-A)

was prepared. m.p. = 155°~157°C, Mass Spec.: MH^+ = 465.

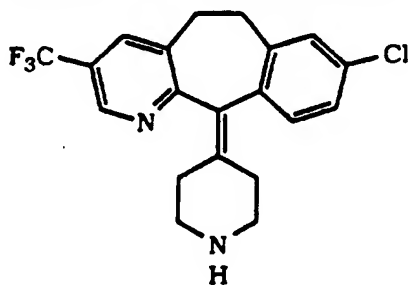
5 Step D:

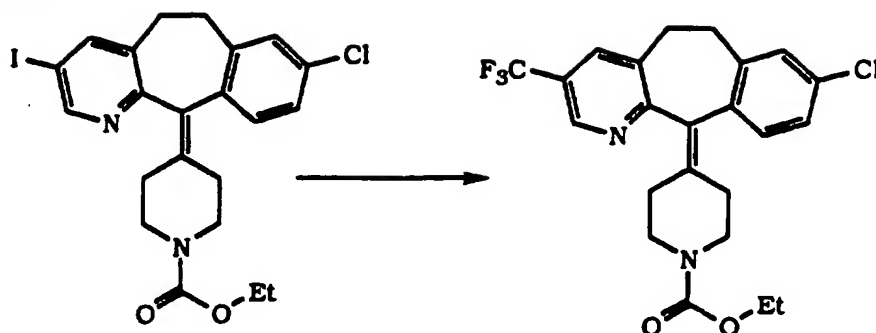


Hydrolyze 1.18 g (2.89 mmol) of the product of Step C via substantially the same procedure as described in Example 358, Step A, of WO 95/10516, to give 0.95 g of the product compound. Mass Spec.: (FAB)

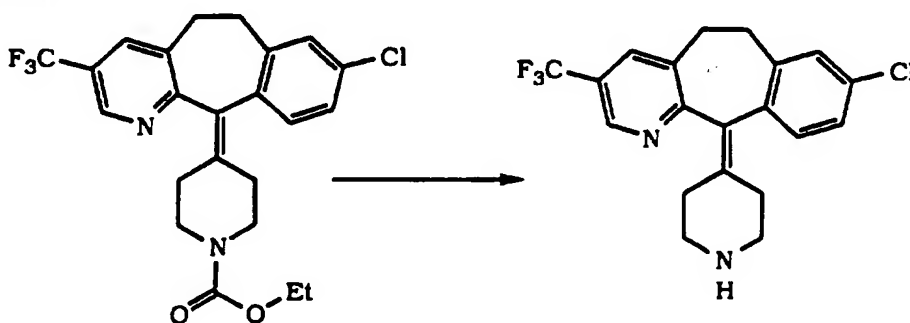
10 MH^+ = 337

PREPARATIVE EXAMPLE 71

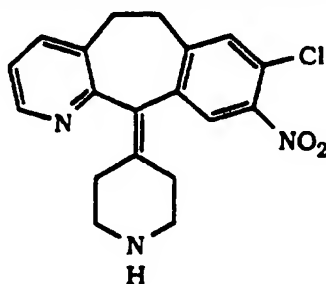


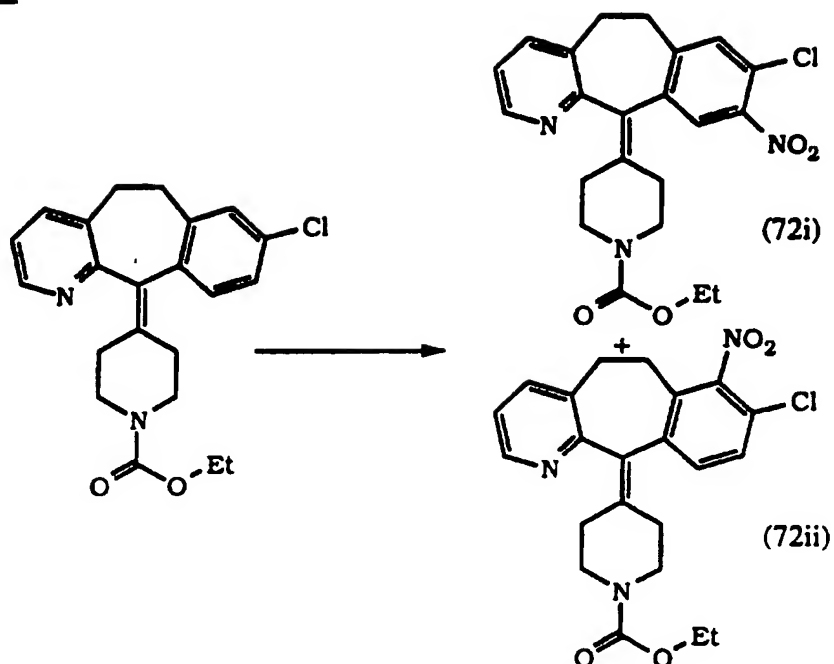
Step A:

Combine 1.01 g (19.9 mmol) of the Product of Preparative Example 48, Step A, 30 mL of DMF, 1.33 g (6.96 mmol) of methyl 2,2-difluoro-2-(fluorosulfonyl)-acetate and 0.75 g (3.97 g) of CuI. Heat the mixture at 60°-80°C for 3 hours, then concentrate to a residue. Dilute the residue with water, extract with CH₂Cl₂, and concentrate *in vacuo* to a residue. Chromatograph (silica gel, 30% EtOAc/hexane, then 10% MeOH/CH₂Cl₂ + NH₄OH) to give 0.15 g of the product compound. Mass Spec.: MH⁺ = 451.1

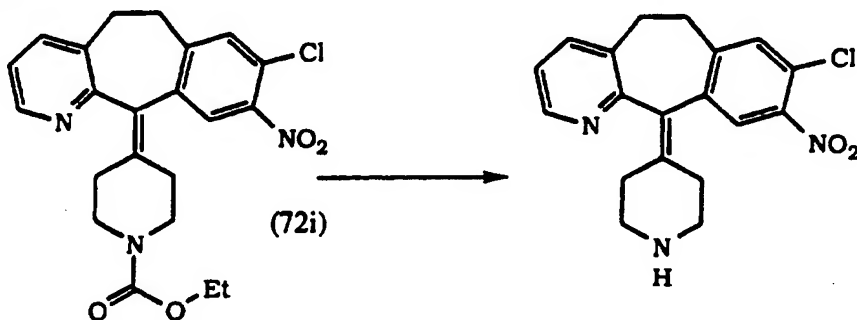
Step B:

Hydrolyze the product of Step A using essentially the same procedure as described in Preparative Example 1, Step G, of WO 95/10516, to give the product compound. Mass Spec.: MH⁺ = 379

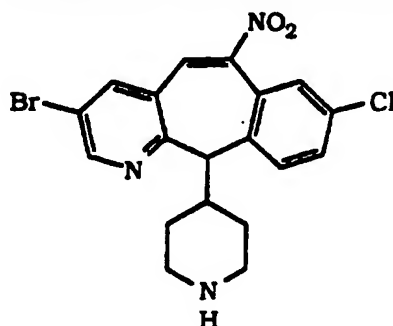
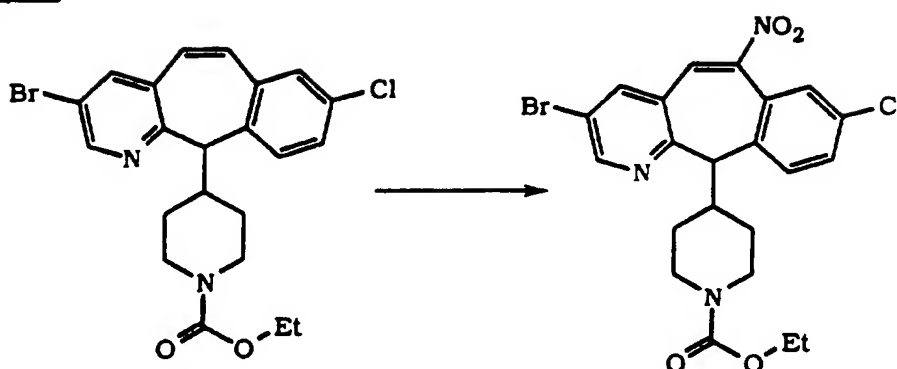
PREPARATIVE EXAMPLE 72

Step A:

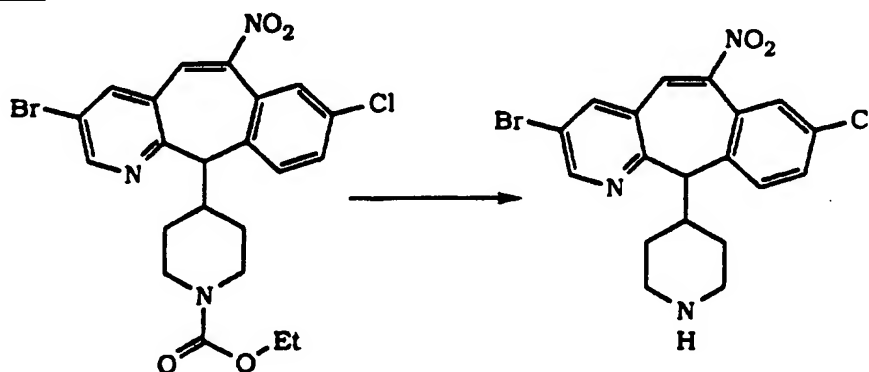
Dissolve 20 g (50 mmol) of the Product of Preparative Example 1, Step F, of WO 95/10516, in 400 mL of concentrated H_2SO_4 , cool to -5°C and add 5.1 g (50 mmol) of KNO_3 in small portions. Stir for 3 hours, cool the mixture and slowly basify with 50% NaOH (aqueous). Extract with CH_2Cl_2 (3 X 500 mL), dry the combined extracts over MgSO_4 , and concentrate *in vacuo* to a residue. Chromatograph (silica gel, 50% EtOAc/hexane) to give 16.33 g of the product compound (72i) and 2.6 g of the product compound (72ii). Mass Spec. (72(i) and (72(ii)): $\text{MH}^+ = 428$

Step B:

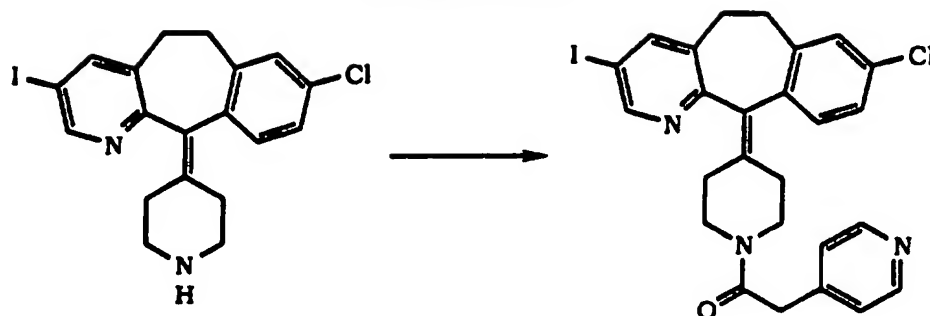
Hydrolyze 5.46 g (12.76 mmol) of the Product of (72i) from Step A, via substantially the same procedure as described for Example 358, Step A, of WO 95/10516, to give 4.34 g of the product compound. Mass Spec.: $\text{MH}^+ = 356$

PREPARATIVE EXAMPLE 73**Step A:**

- 5 Combine 1.6 g of the Product (54i) of Preparative Example 54, Step B, 12 mL of CH₂Cl₂, and 1.16 g of tetrabutylammonium nitrate, cool to 0°C and slowly add (dropwise) a solution of 0.8 g of TFAA in 2 mL of CH₂Cl₂. Stir for 6 hours at 0°C, let the mixture stand at 0°C overnight, then wash successively with saturated NaHCO₃ (aqueous), water and brine, and dry
- 10 over Na₂SO₄. Concentrate *in vacuo* to a residue, then chromatograph (silica gel, 30% EtOAc/hexane) to give 0.38 g of the product compound.

Step B:

- 15 Hydrolyze 0.38 g of the Product of Step A via substantially the same procedure as described for Example 358, Step A, of WO 95/10516, to give 0.235 g of the product compound.

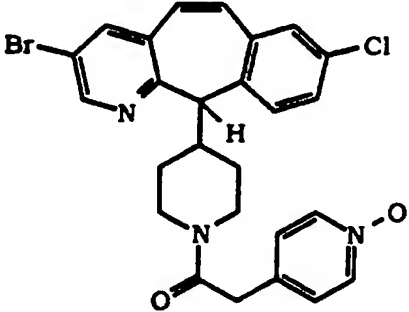
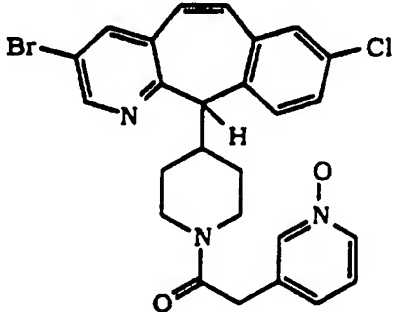
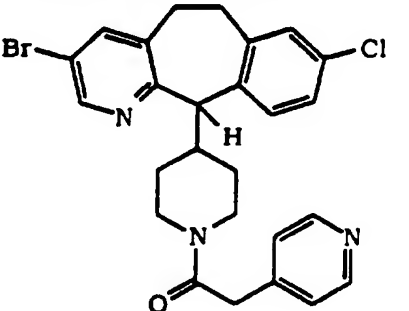
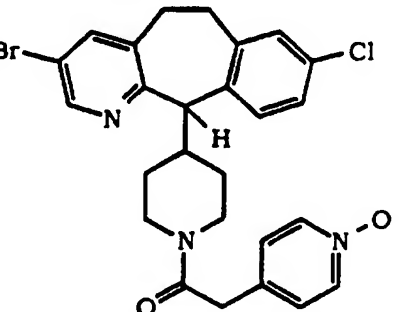
EXAMPLE 400

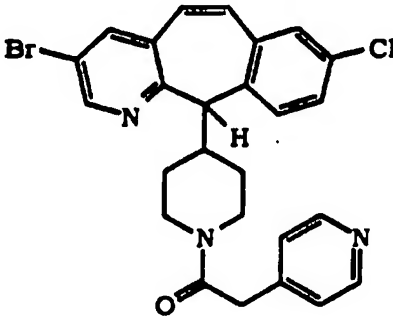
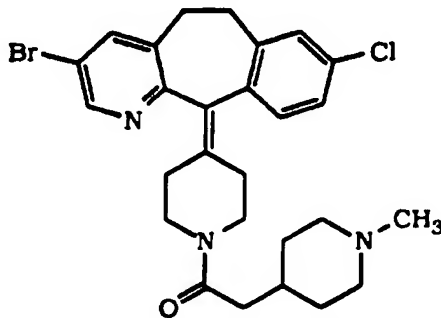
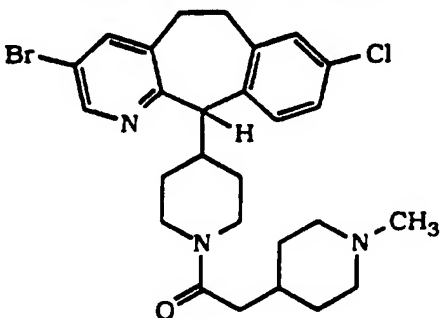
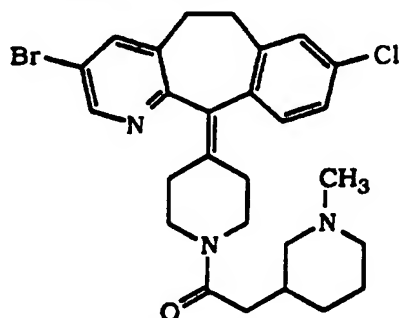
The product of Preparative Example 48, Step B, is reacted with 4-pyridyl acetic acid via essentially the same procedure as described in Example 180, of WO 95/10516, to give the product compound (5.210).
 Mass Spec.: $MH^+ = 556$

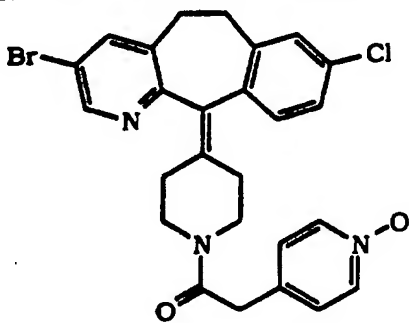
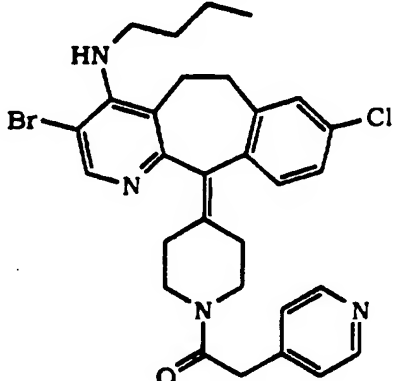
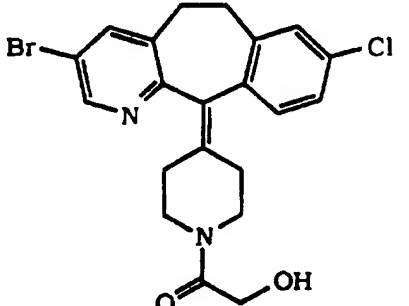
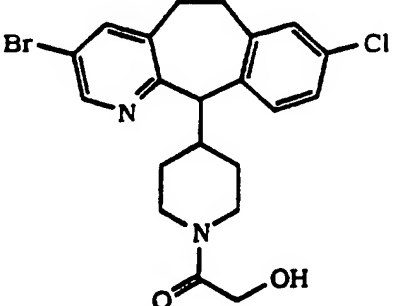
Using the appropriate carboxylic acid and the starting compound indicated, the compounds in Table 2 were prepared via substantially the same procedure as described for Example 400:

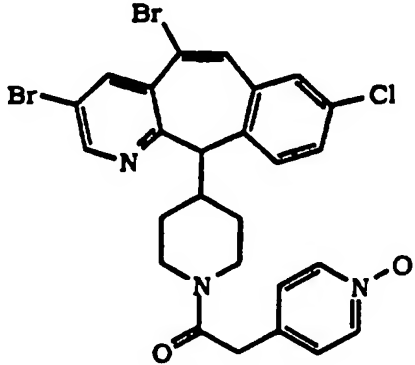
TABLE 2

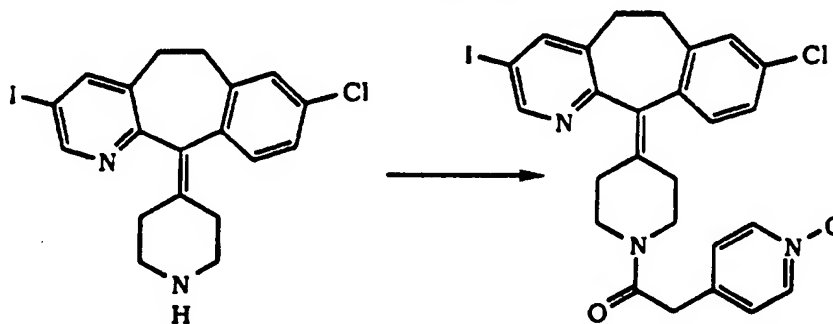
Starting Compound	Product Compound	Analytical Data
Preparative Example 49	 Example 400-A	Mass Spec: $MH^+ = 458$
Preparative Example 53C	 Example 400-B (5.203)	Mass Spec.: $MH^+ = 528.2$

Preparative Example 53C	 Example 400-C (5.200)	Mass Spec.: $MH^+ = 524.2$
Preparative Example 53C	 Example 400-D (5.217)	Mass Spec.: $MH^+ = 524.1$
Preparative Example 51A	 Example 400-E (5.208)	Mass Spec.: $MH^+ = 512.1$
Preparative Example 51A	 Example 400-F (5.201)	Mass Spec.: $MH^+ = 528$

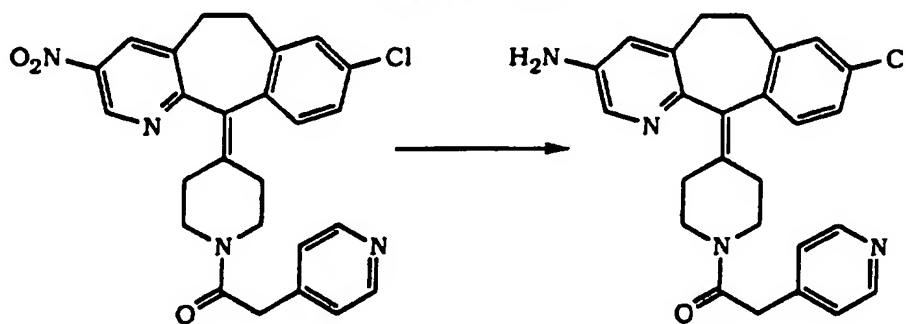
Preparative Example 53C	 Example 400-G (5.204)	Mass Spec.: $MH^+ = 508.0$
Preparative Example 49	 Example 400-H (5.220)	Mass Spec.: $MH^+ = 530.2$
Preparative Example 51A	 Example 400-J (5.212)	Mass Spec.: $MH^+ = 532.3$
Preparative Example 49	 Example 400-K (5.218)	Mass Spec.: $MH^+ = 530.2$

Preparative Example 49	 Example 400-L (5.206)	Mass Spec.: $MH^+ = 526$
Preparative Example 56, Step C	 Example 400-M	Mass Spec.: $MH^+ = 581$
Preparative Example 49	 Example 400-N	Mass Spec.: $MH^+ = 449.2$
Preparative Example 51A	 Example 400-P	m.p. = 62.8°- 63.5°C Mass Spec.: $MH^+ = 451$

<p>Preparative Example 53B</p>	 <p>Example 400-Q</p>	<p>Mass Spec.: MH⁺ = 602</p>
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EXAMPLE 401

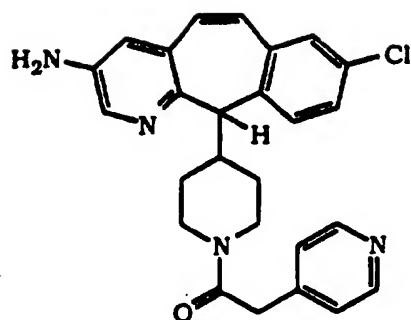
The product of Preparative Example 48, Step B, is reacted with 4-pyridyl acetic acid N-oxide via essentially the same procedure as described in Example 227 to give the product compound (5.209).
 5 Mass Spec.: MH⁺ = 572

EXAMPLE 402

The product of Example 358, Step B, of WO 95/10516, is reduced via essentially the same procedure as described in Step B of Preparative Example 47, of WO 95/10516, to give the product compound. mp=133.2-133.4 °C MH⁺ 445
 10

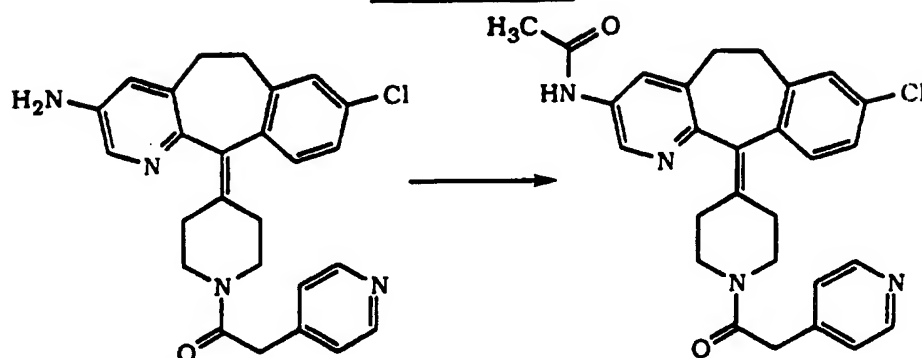
Using the compound of Example 411-B, and following substantially the same procedure as described for Example 402, the compound:

- 66 -

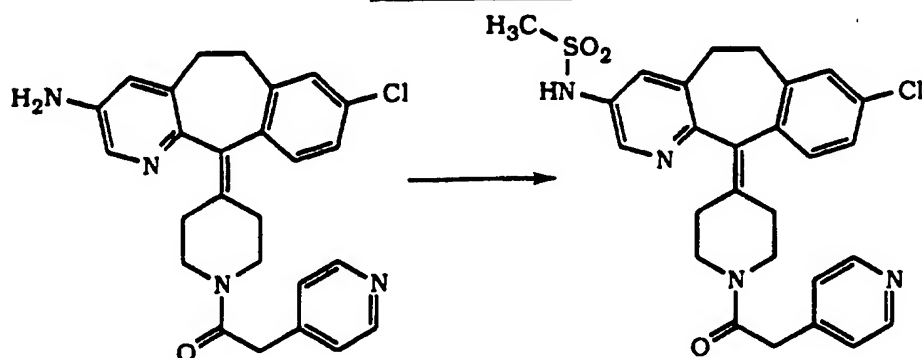


(Example 402-A)

was prepared. Mass Spec.: $MH^+ = 445.2$

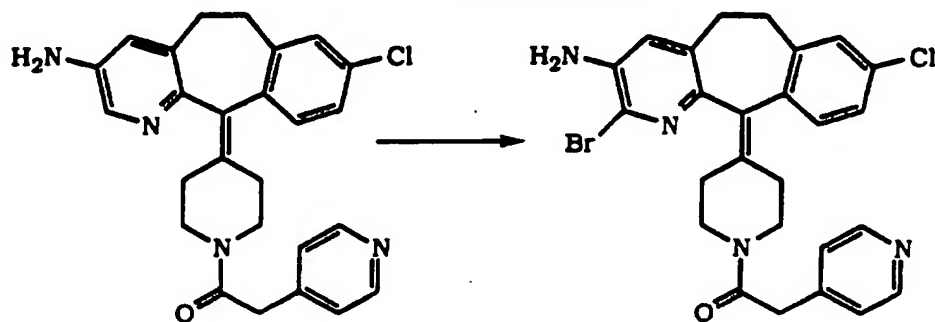
EXAMPLE 403

- 5 Combine 0.3 g (0.67 mmol) of the product of Example 402, 5 mL of pyridine and 0.1 g (1.01 mmol) of acetic anhydride and stir the mixture at room temperature for 2 days. Add another 100 μ L of acetic anhydride, warm to 60°C and stir for 6h. Neutralize the reaction mixture then basify with 1 N NaOH (aqueous) to pH = 10. Extract with CH_2Cl_2 , dry the extract
- 10 over $MgSO_4$ and concentrate to a residue. Purify the residue by HPLC eluting 8% MeOH/ CH_2Cl_2 + concentrated NH_4OH (aqueous) to give 0.22 g of the product compound. Mass Spec.: $MH^+ = 487$

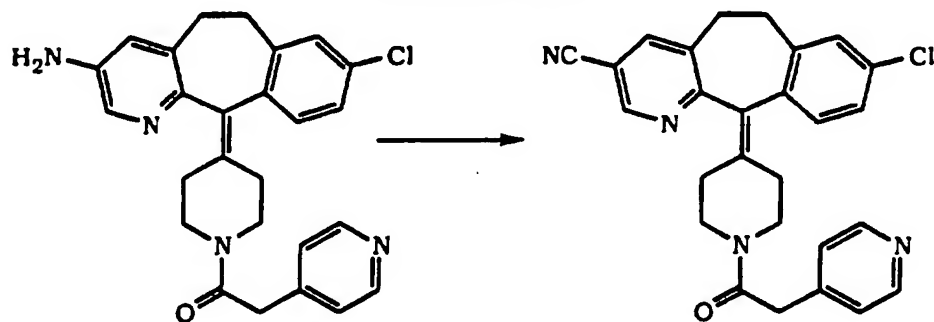
EXAMPLE 404

The product of Example 402 is reacted with methanesulfonyl chloride via substantially the same procedure as described for Example 403 to give the 0.32 g of the product compound. Mass Spec.: $MH^+ = 523$

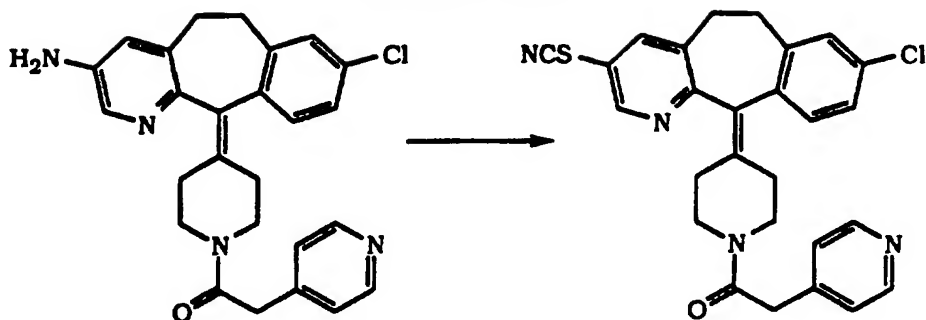
5

EXAMPLE 405

Combine 1.5 g (3.37 mmol) of the product of Example 402 and 10 mL of AcOH, then add 3.37 mL of a solution of bromine in AcOH and stir the mixture at room temperature overnight. Basify the mixture with 1N NaOH (aqueous) to basic pH, then extract with EtOAc. Concentrate the extract to a residue and chromatograph (silica gel, 90% EtOAc/hexane, then 5% Et₃N/EtOAc) to give the product compound. Mass Spec.: $MH^+ = 525$.

EXAMPLE 406

Combine 0.5 g (1.12 mmol) of the product of Example 402 and 10 mL of acetone, add 230 μ L of conc. HCl (aqueous) and 4 mL of water, and cool to -10°C . Add a solution of 0.085 g NaNO₂ in 4 mL of water, stir for 15 min., then add the reaction mixture to a solution of CuCN [freshly prepared by adding 0.336 g (1.34 mmol) of CuSO₄ in 2 mL of water to H₂O a solution of 0.365 g (5.6 mmol) of KCN in 2 mL of H₂O]. Heat the mixture to 60°C - 70°C , then at 70°C - 80°C to remove acetone. Cool the mixture and dilute with H₂O, then exhaustively extracted with CH₂Cl₂. Concentrate the extracts to a residue then purify by HPLC using 3 % methanolic ammonia in CH₂Cl₂ to give 0.25 g (50% yield) of the product compound. Mass Spec.: $MH^+ = 455$.

EXAMPLE 407

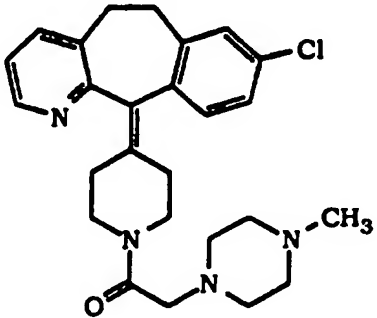
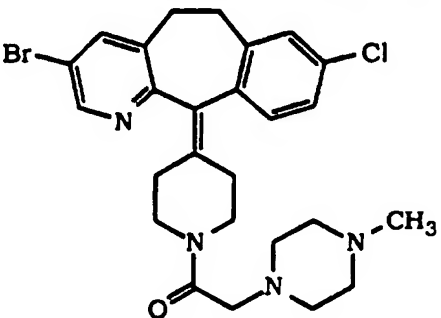
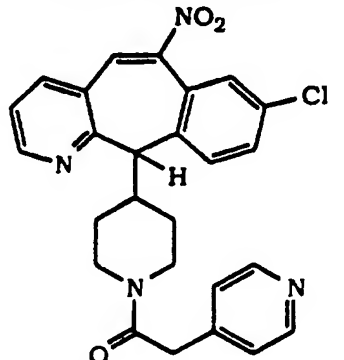
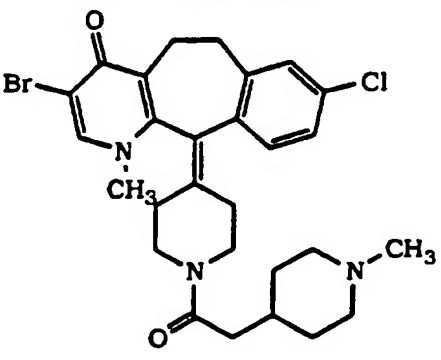
Combine 0.55 g (1.25 mmol) of the product of Example 402 and 50 mL of dilute H₂SO₄ at room temperature. Cool the mixture to -10°C, add a solution of 0.092 g of NaNO₂ in 5 mL of water was added and stir for 15 min. Slowly add a solution of 0.46 g (4.7 mmol) of KSCN and 0.3 g (2.49 mmol) of CuSCN in 15 mL of water over a period of 0.5 hours. Stir for 0.5 hour then heat at reflux for 15 min. Cool the mixture and adjust the pH to -7, then extract with CH₂Cl₂. Concentrate the extracts to a residue and chromatograph (silica gel, 3% MeOH/CH₂Cl₂ + NH₄OH) to give the product compound. Mass Spec.: MH⁺ = 487

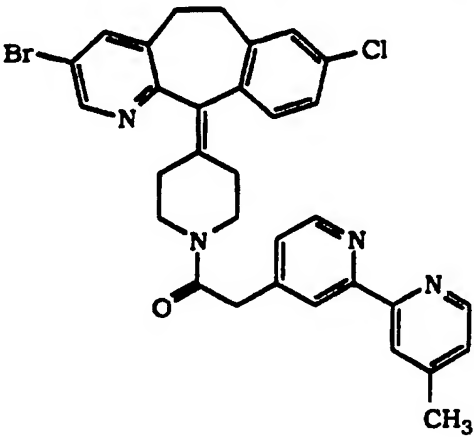
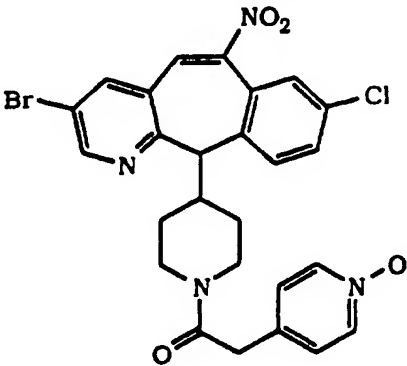
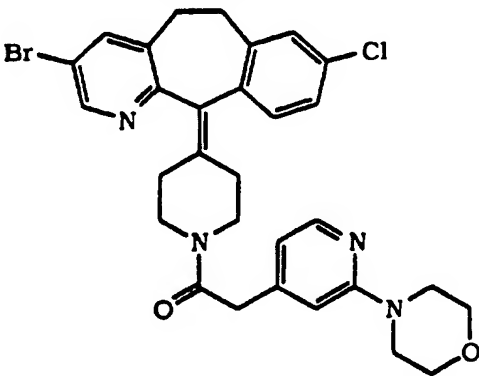
EXAMPLE 410

Using the appropriate carboxylic acid and the starting compound indicated, the compounds in Table 3 were prepared via substantially the same procedure as described in Example 180 of WO 95/10516:

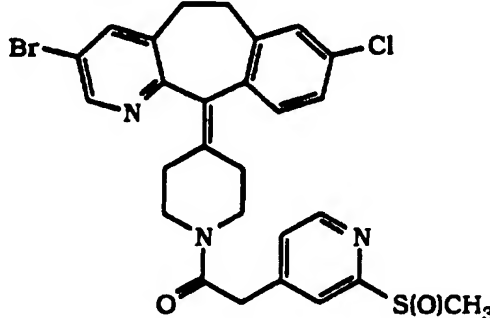
TABLE 3

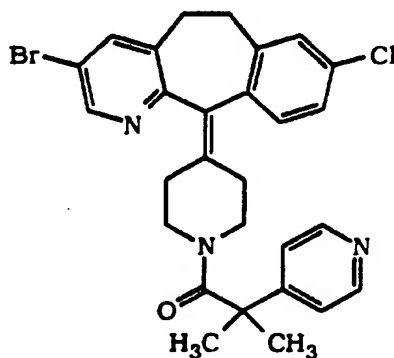
Starting Compound	Product Compound	Analytical Data
Preparative Example 49	<p>Example 410-G</p>	<p>m.p. = 137°-138°C</p> <p>Mass Spec.: MH⁺ = 565</p>

Preparative Example 1 of WO 95/10516	 Example 410-H	Mass Spec.: $MH^+ = 451.2$
Preparative Example 49	 Example 410-J	Mass Spec.: $MH^+ = 531.2$
Preparative Example 53	 Example 410-L	Mass Spec.: $MH^+ = 475.2$
Preparative Example 57	 Example 410-M	m.p. = 151°- 153°C Mass Spec.: $MH^+ = 560$

Preparative Example 49	 Example 410-Q	m.p. = 102.6°- 103°C Mass Spec.: MH ⁺ = 601.2
Preparative Example 73	 Example 410-R	Mass Spec.: MH ⁺ = 569
Preparative Example 49	 Example 410-S	m.p. = 97°C (dec.) Mass Spec.: MH ⁺ = 595

Preparative Example 49	 Example 410-T	m.p.= 132.6°C (dec.) Mass Spec.: MH ⁺ = 576
Preparative Example 49	 Example 410-U	m.p.= 111.2°C (dec.) Mass Spec.: MH ⁺ = 608
Preparative Example 49	 Example 410-V	m.p.= 85.1°C (dec.) Mass Spec.: MH ⁺ = 556
Preparative Example 49	 Example 410-W	m.p.= 114°C (dec.) Mass Spec.: MH ⁺ = 588

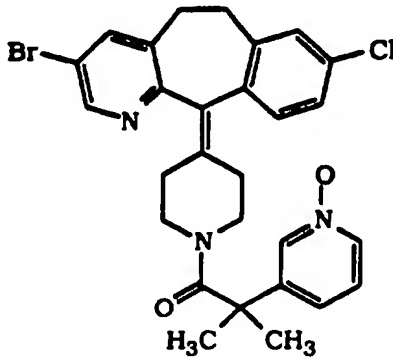
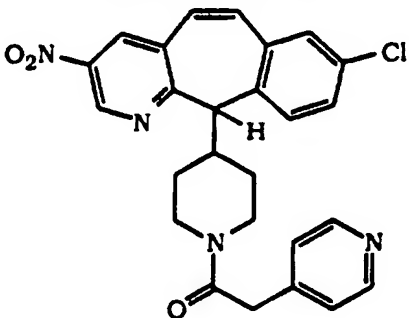
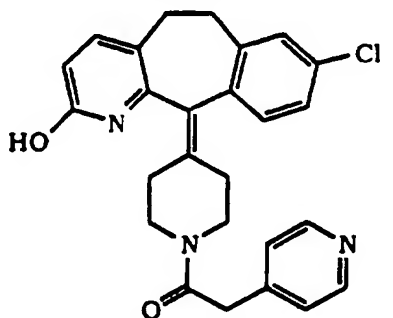
Preparative Example 49	 <p>Example 410-X</p>	m.p.= 122.5°- 126.0°C Mass Spec.: MH ⁺ = 572
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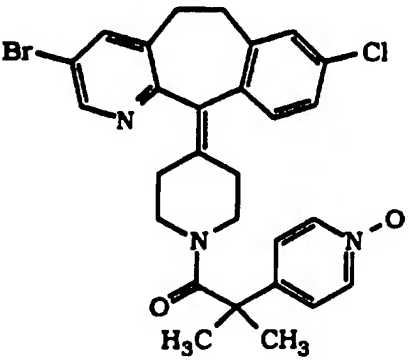
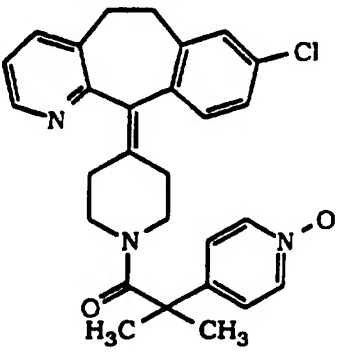
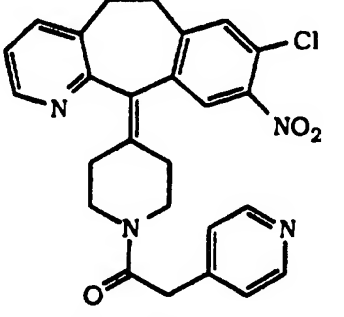
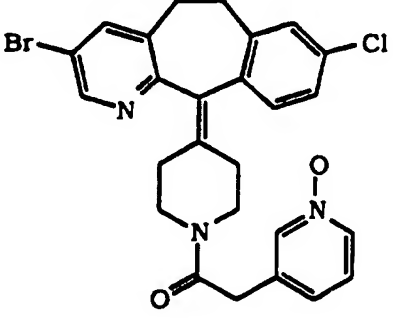
EXAMPLE 411

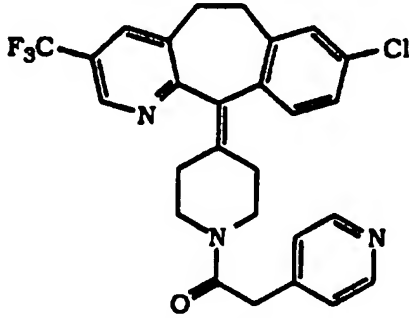
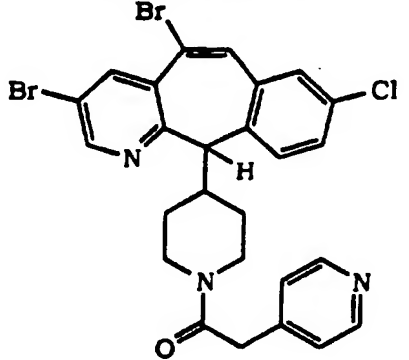
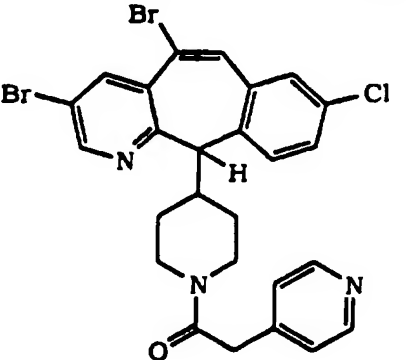
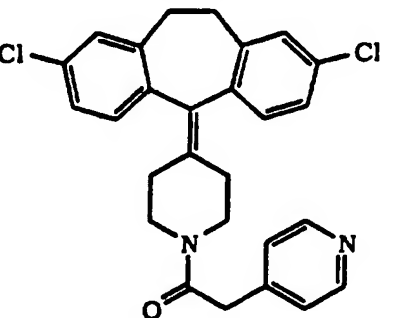
5 The product of Preparative Example 49 was reacted with 2-methyl-2-(4-pyridyl)propanoic acid via substantially the same procedure as described for Example 180, of WO 95/10516, to give the product compound. Mass Spec.: MH⁺ = 538

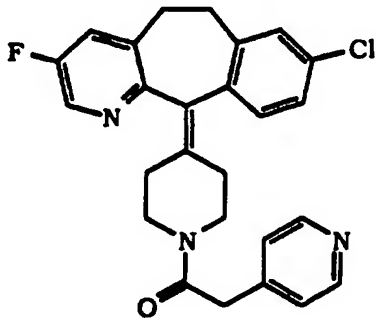
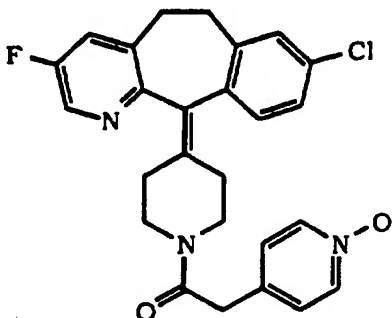
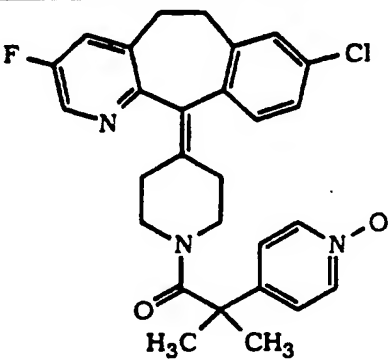
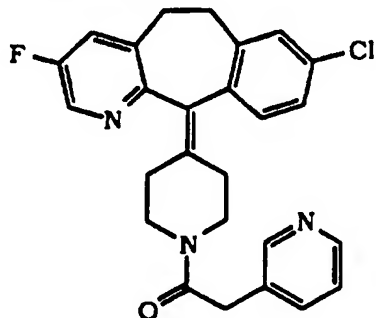
10 Using the appropriate carboxylic acid (or carboxylate salt, e.g. lithium carboxylate) and the starting compound indicated, the compounds in Table 4 were prepared via substantially the same procedure as described for Example 410:

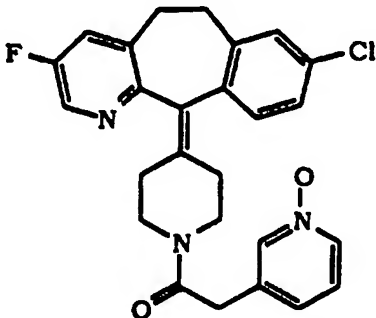
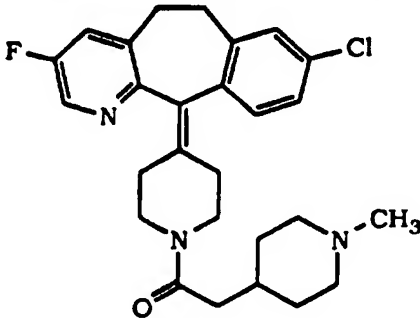
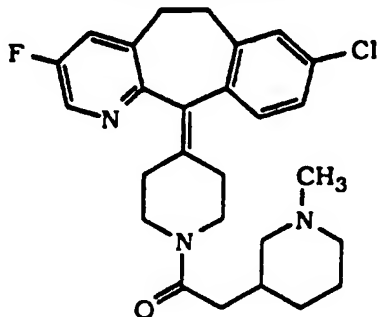
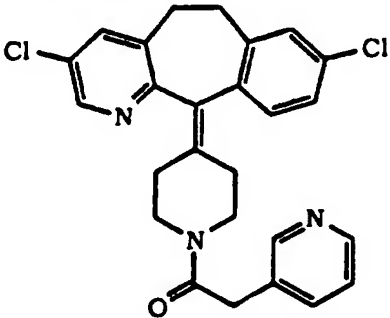
TABLE 4

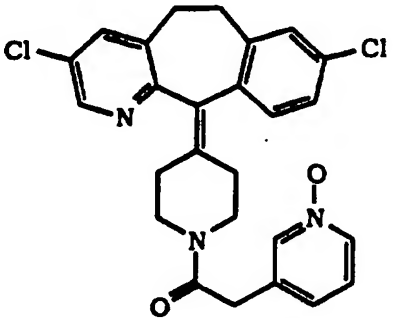
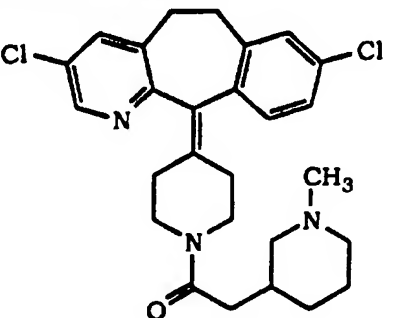
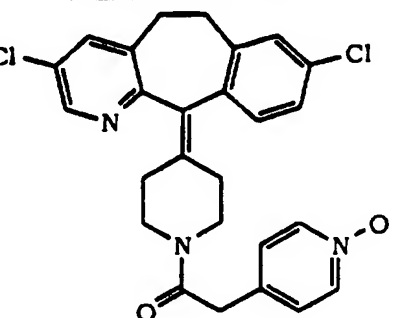
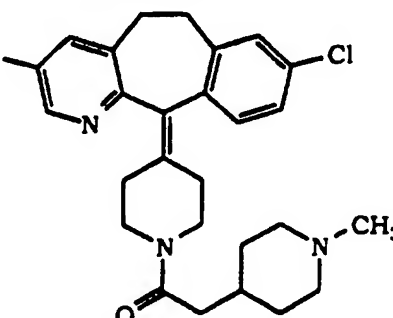
Starting Compound	Product Compound	Analytical Data
Preparative Example 49	 Example 411-A	Mass Spec.: $MH^+ = 554$
Preparative Example 53A	 Example 411-B	Mass Spec.: $MH^+ = 475.2$
Preparative Example 55	 Example 411-C	m.p. = 155.2°- 158.9°C Mass Spec.: $MH^+ = 446$

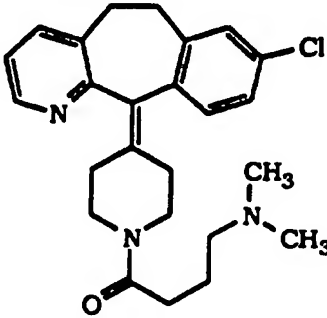
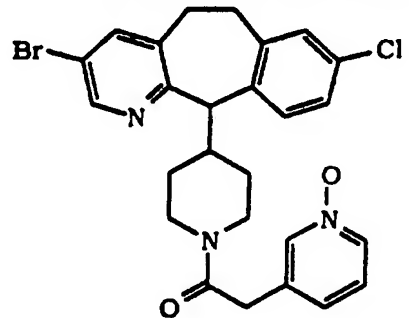
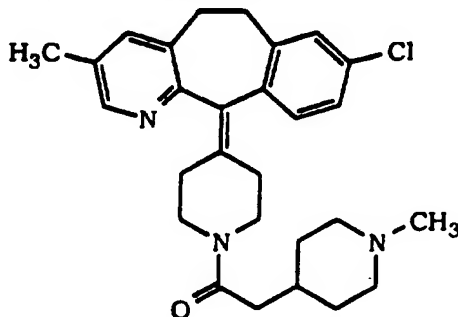
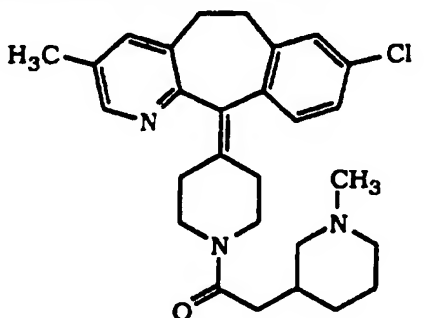
Preparative Example 49	 <p>Example 411-D</p>	Mass Spec.: $MH^+ = 554$
Preparative Example 1 of WO 95/10516	 <p>Example 411-E</p>	Mass Spec.: $MH^+ = 474$
Preparative Example 72	 <p>Example 411-F</p>	Mass Spec.: $MH^+ = 475$
Preparative Example 49	 <p>Example 411-G</p>	Mass Spec.: $MH^+ = 526.1$

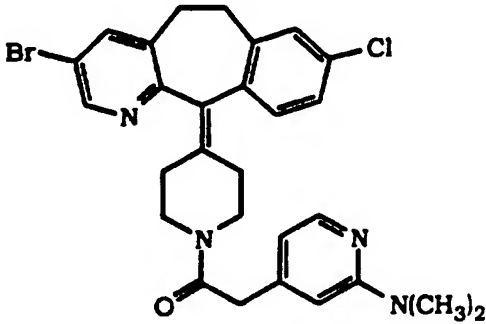
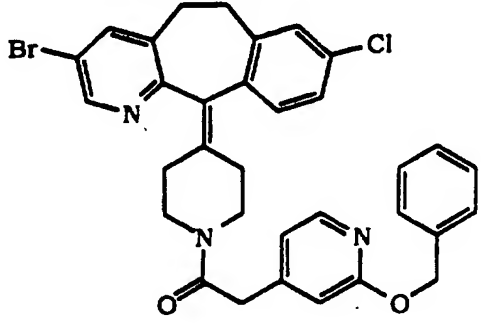
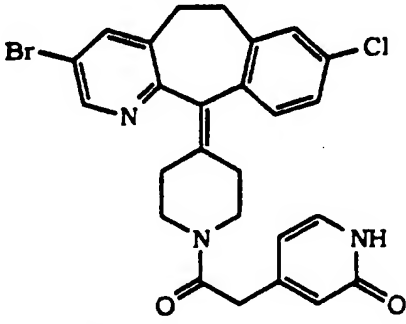
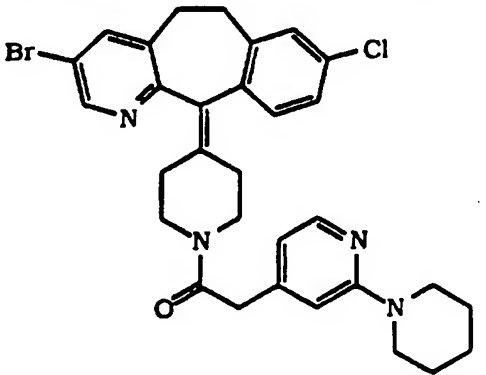
Preparative Example 71	 Example 411-H	Mass Spec.: MH ⁺ = 498
Preparative Example 53B	 Example 411-J	Mass Spec.: MH ⁺ = 536
Preparative Example 53B	 Example 411-K	Mass Spec.: MH ⁺ = 581
Preparative Example 59	 Example 411-L	m.p. = 97°- 98°C Mass Spec.: (FAB) MH ⁺ = 463.1

Preparative Example 60	 Example 411-M	Mass Spec.: MH ⁺ = 448
Preparative Example 60	 Example 411-N	Mass Spec.: MH ⁺ = 464
Preparative Example 60	 Example 411-O	Mass Spec.: MH ⁺ = 492
Preparative Example 60	 Example 411-P	Mass Spec.: MH ⁺ = 448

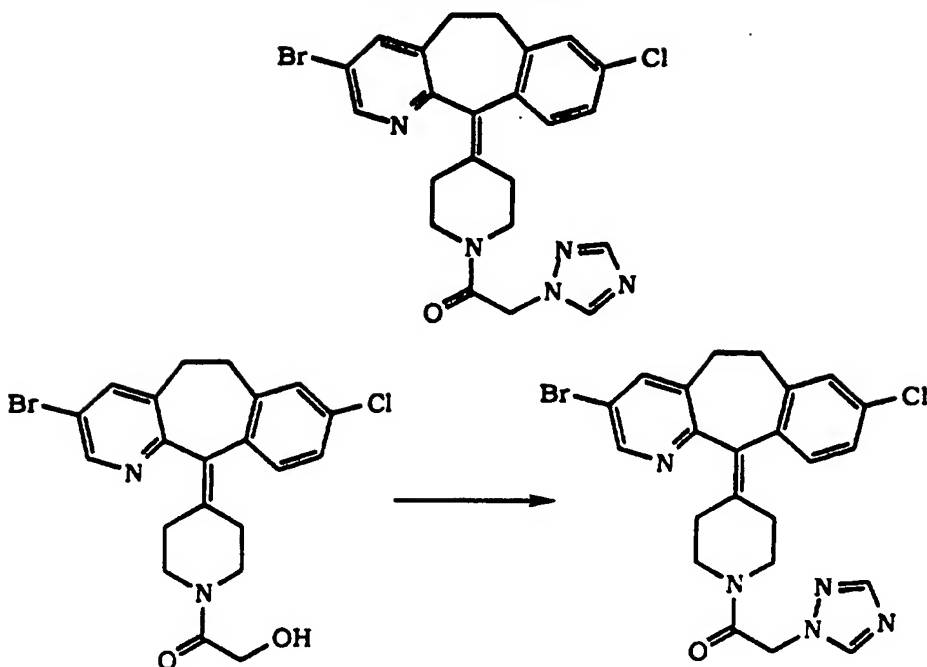
Preparative Example 60	 Example 411-Q	Mass Spec.: $MH^+ = 464$
Preparative Example 60	 Example 411-R	Mass Spec.: $MH^+ = 469$
Preparative Example 60	 Example 411-S	Mass Spec.: $MH^+ = 469$
Preparative Example 60A	 Example 411-T	Mass Spec.: $MH^+ = 465$

Preparative Example 60A	 Example 411-U	Mass Spec.: MH ⁺ = 481
Preparative Example 60A	 Example 411-V	Mass Spec.: MH ⁺ = 485
Preparative Example 60A	 Example 411-W	Mass Spec.: MH ⁺ = 481
Preparative Example 60A	 Example 411-X	Mass Spec.: MH ⁺ = 485

Preparative Example 1 Step G of WO 95/10516	 Example 411-Z	-----
Preparative Example 51A	 Example 411-AA	m.p. = 125°- 125.4°C Mass Spec.: MH ⁺ = 528
Preparative Example 3 Step E of WO 95/10516	 Example 411-BB	m.p. = 186.6°- 187°C Mass Spec.: MH ⁺ = 464
Preparative Example 3 Step E of WO 95/10516	 Example 411-CC	Mass Spec.: MH ⁺ = 464

Preparative Example 49	 Example 411-DD	m.p. = 80.2°C (dec.) Mass Spec.: MH ⁺ = 553
Preparative Example 49	 Example 411-EE	m.p. = 83°- 86°C Mass Spec.: MH ⁺ = 616
Preparative Example 49	 Example 411-FF	m.p. = 167°- 171°C Mass Spec.: MH ⁺ = 526
Preparative Example 49	 Example 411-GG	m.p. = 134°- 140°C Mass Spec.: MH ⁺ = 593

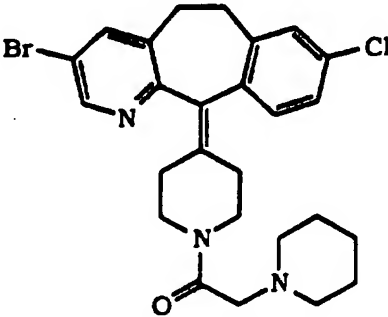
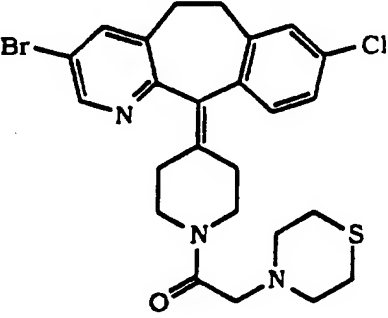
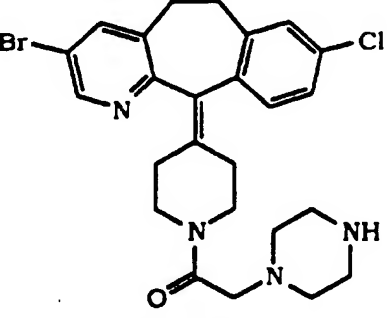
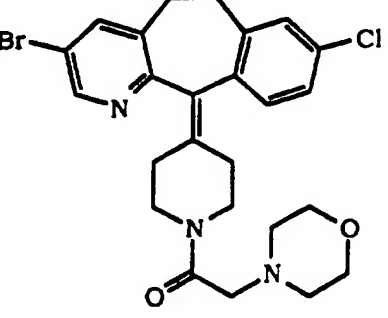
- 81 -

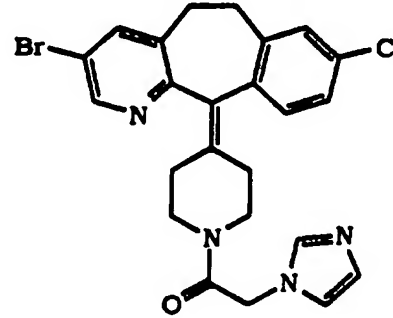
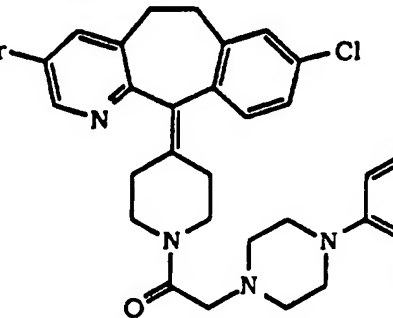
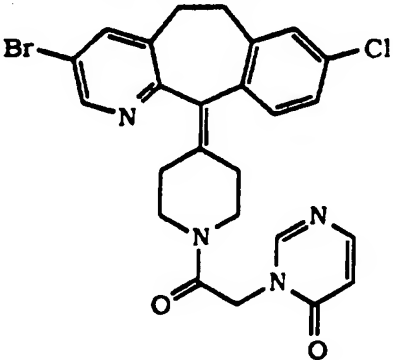
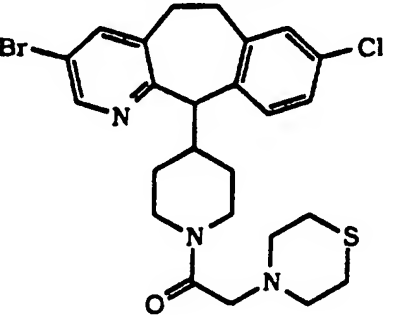
EXAMPLE 412

Combine 50 mg (0.11 mmol) of the compound of Example 400-N,
5 and 1.5 mL of SOCl_2 and stir at room temperature overnight. Concentrate *in vacuo* to a residue, add 2.0 mL of DMF to the residue, then add 20 mg (0.2 mmol) of 1,2,4-triazole sodium salt and heat to 100°C overnight. Cool the mixture, concentrate *in vacuo* to remove most of the solvent, wash with water (3 times), then dry the residue over Na_2SO_4 . Concentrate *in vacuo* to a residue and chromatograph (silica gel, 75% (10% NH_4OH in MeOH) in CH_2Cl_2) to give 26 mg of the product compound. Mass Spec.: $\text{MH}^+ = 498$
10

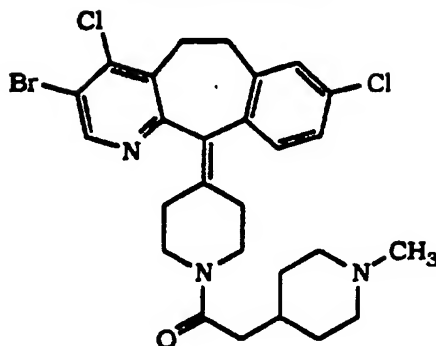
Using the appropriate starting compound and substantially the same procedure as described for Example 412, but substituting the amine
15 nucleophile indicated in place of the 1,2,4-triazole sodium salt, the compounds in Table 5 were prepared:

TABLE 5

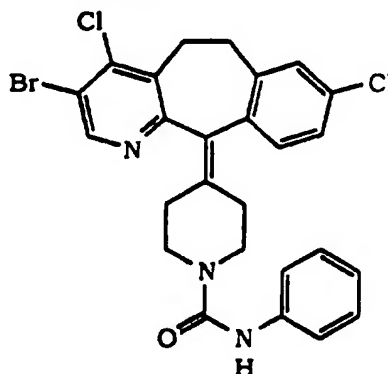
Amine Nucleophile	Product Compound	Analytical Data
<p>piperidine</p> <p>(solvent is CH₂Cl₂ instead of DMF)</p>	 <p>Example 412-A</p>	<p>Mass Spec.: MH⁺ = 514.2</p>
<p>thiomorpholine</p> <p>(solvent is CH₂Cl₂ instead of DMF)</p>	 <p>Example 412-B</p>	<p>Mass Spec.: MH⁺ = 532.1</p>
<p>piperazine</p> <p>(solvent is CH₂Cl₂ instead of DMF)</p>	 <p>Example 412-C</p>	<p>Mass Spec.: MH⁺ = 515</p>
<p>morpholine</p> <p>(solvent is CH₂Cl₂ instead of DMF)</p>	 <p>Example 412-D</p>	<p>Mass Spec.: MH⁺ = 516.1</p>

<p>imidazole</p> <p>(solvent is CH₂Cl₂ instead of DMF)</p>	 <p>Example 412-E</p>	<p>Mass Spec.: MH⁺ = 497.2</p>
<p>N-(2-methyl- phenyl)- piperazine</p> <p>(solvent is CH₂Cl₂ instead of DMF)</p>	 <p>Example 412-F</p>	<p>Mass Spec.: MH⁺ = 605.1</p>
<p>4(3H)- pyrimidone</p>	 <p>Example 412-G</p>	<p>Mass Spec.: MH⁺ = 525.1</p>
<p>thiomorpholine</p>	 <p>Example 412-H</p>	<p>m.p. = 105°- 105.6°C Mass Spec.: MH⁺ = 536</p>

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EXAMPLE 413

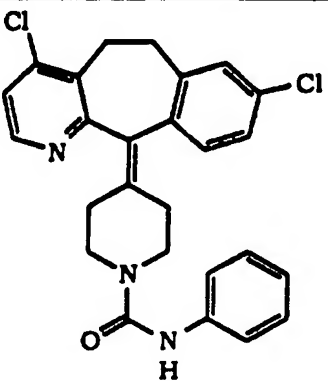
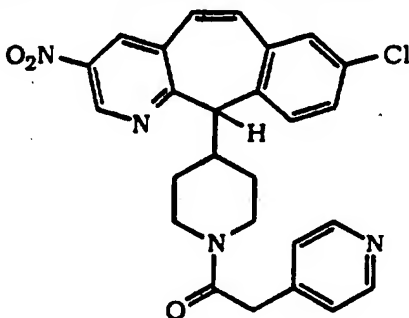
Combine 0.32 g of the product from Preparative Example 46, of WO 95/10516 and 2 mL of anhydrous CH_2Cl_2 and add 6 mL of a mixture of
5 4.17 g of N-methyl-4-piperidylacetic acid, 1.03 mL of methanesulfonyl chloride, 6.83 mL of Et_3N and 50 mL of CH_2Cl_2 . Stir at 25°C overnight, then add 1 N NaOH (aqueous) and shake well. Separate the layers, dry the organic phase over MgSO_4 , and concentrate to a residue. Chromatograph the residue (silica gel, 3% MeOH/ CH_2Cl_2 + NH_4OH) to
10 give 0.19 g (45% yield) of the product compound. m.p. = 105°C (dec); Mass Spec.: $\text{MH}^+ = 564$.

EXAMPLE 414

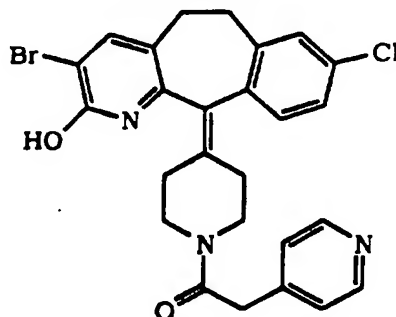
Combine 84 mg of the product from Preparative Example 46, of WO
15 95/10516, 5 mL of pyridine and 0.04 mL of phenylisocyanate and stir at 25°C for 48 hours. Concentrate *in vacuo* to a residue, dilute with CH_2Cl_2 and wash with saturated NaHCO_3 (aqueous). Dry over MgSO_4 , concentrate to a residue and chromatograph (silica gel, 50-70% hexane/ EtOAc) to give 14 mg (13% yield) of the product compound. m.p.
20 = 125.6°C (dec); Mass Spec.: $\text{MH}^+ = 544$

Using the starting compound indicated, the compounds in Table 6 were prepared via substantially the same procedure as described for Example 414:

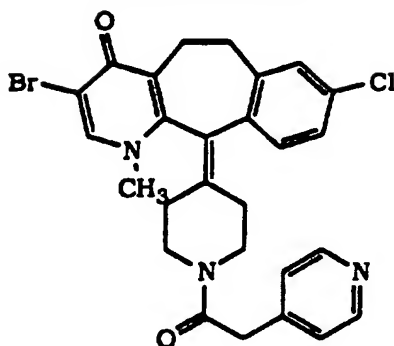
TABLE 6

Starting Compound	Product Compound	Analytical Data
Preparative Example 28 of WO 95/10516	 Example 414-A	m.p. = 131.8°C (dec.) Mass Spec.: MH ⁺ = 464
Preparative Example 53A	 Example 414-B	Mass Spec.: MH ⁺ = 475.2

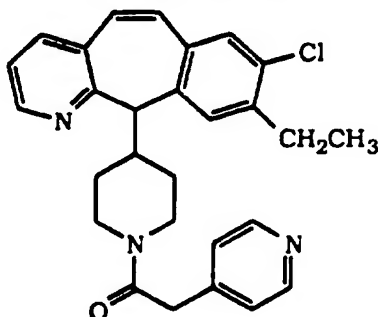
EXAMPLE 415



- Combine 0.64 g of the product from Example 411-C and 16 mL of glacial HOAc, and add 15 mL of a 0.54 M solution of bromine in HOAc at 25°C under N₂. After 10 minutes, pour the mixture into water, filter to collect the resulting solid, and wash with water. Dry the solid under vacuum, then chromatograph (silica gel, 6-15% MeOH/CH₂Cl₂) to give 0.26 grams (35% yield) of the product compound. m.p. = 150.0 °C (dec), Mass Spec.: MH⁺ = 526

EXAMPLE 416

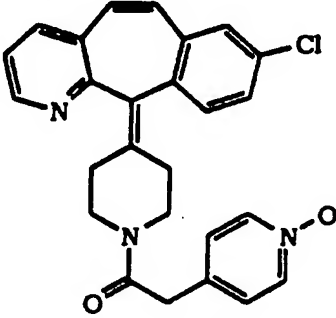
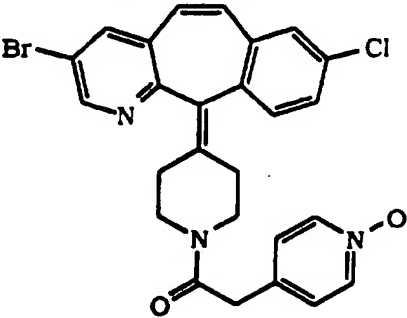
- Combine 0.33 g of the product from Preparative Example 57, 2 mL of anhydrous CH_2Cl_2 , and 10 mL of a mixture of 7.20 g of 4-pyridylacetic acid hydrochloride, 1.61 mL of methanesulfonylchloride, 27 mL of Et_3N and 60 mL of CH_2Cl_2 , and stir at 25 °C for 48 hours. Dilute the mixture with CH_2Cl_2 , wash with saturated NaHCO_3 (aqueous), then with brine. Dry over MgSO_4 , concentrate to a residue and chromatograph (silica gel, 5% $\text{MeOH}/\text{CH}_2\text{Cl}_2$ + NH_4OH) to give 0.23 g (55% yield) of the product compound. m.p. = 142 °C (dec); Mass Spec.: $\text{MH}^+ = 540$

EXAMPLE 417

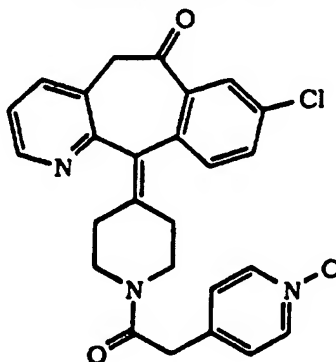
- React the product from Preparative Example 35, of WO 95/10516, with 4-pyridylacetic acid via substantially the same procedure as described for Example 266, of WO 95/10516, to give the product compound. Mass Spec.: $\text{MH}^+ = 458$

Using the appropriate carboxylic acid and the starting compound indicated, the compounds in Table 7 were prepared via substantially the same procedure as described for Example 417:

TABLE 7

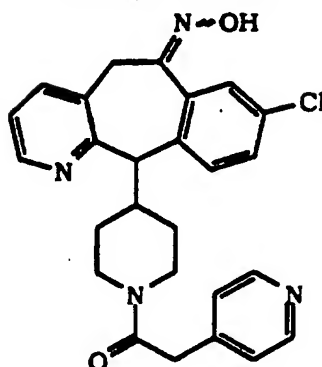
Starting Compound	Product Compound	Analytical Data
Preparative Example 37B of WO 95/10516	 Example 417-A	Mass Spec.: MH ⁺ = 444
Preparative Example 58	 Example 417-B	Mass Spec.: MH ⁺ = 522

EXAMPLE 418



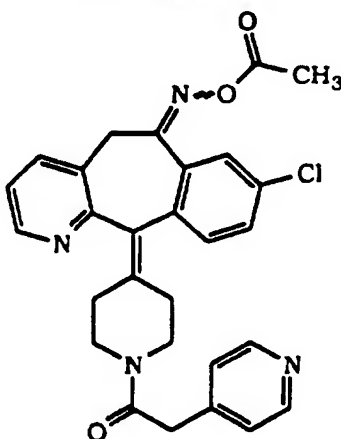
Following the procedure of Example 283, of WO 95/10516, except
 5 using 4-pyridylacetic acid N-oxide gave the product compound. Mass
 Spec.: MH⁺ = 460

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EXAMPLE 419

Dissolve 4.01 g (8.42 mmol) of the compound of Example 410-L in EtOAc and add 14.25 g (63.1 mmol) of finely powdered SnCl_2 dihydrate and stir the mixture for 5 hours. Add 150 mL of saturated NaF (aqueous) and stir for 15 min, then separate the layers and dry the organic phase over MgSO_4 . Filtration and concentrate *in vacuo* to a residue, then chromatograph (silica gel, 95% $\text{CH}_2\text{Cl}_2/\text{MeOH} + \text{NH}_4\text{OH}$) to give 2.95 g of the product compound. Mass Spec.: $\text{MH}^+ = 461$

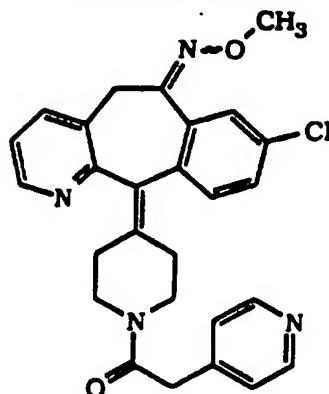
10

EXAMPLE 420

Combine 0.50 g (1.08 mmol) of the compound of Example 419 and 10 mL of anhydrous CH_2Cl_2 , and add 0.11 mL (1.62 mmol) of CH_3COCl . Add 0.34 mL (4.32 mmol) of pyridine and stir at room temperature for 2.5 hours. Dilute the mixture with saturated NaHCO_3 (aqueous), extract with CH_2Cl_2 , wash the extracts with brine and dry over MgSO_4 . Concentrate *in vacuo* to a residue and chromatograph (silica gel, 10% $\text{MeOH}/\text{CH}_2\text{Cl}_2 + \text{NH}_4\text{OH}$) to give 0.271 g of the product compound. Mass Spec.: $\text{MH}^+ = 503$

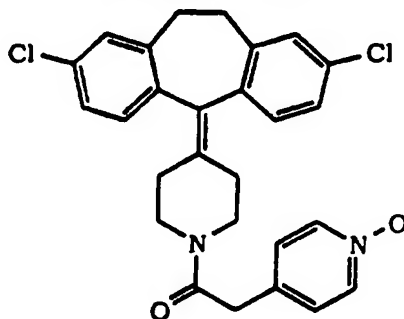
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EXAMPLE 421

Combine 0.65 g (1.41 mmol) of the product compound of Example 419, 20 mL of CH₂Cl₂, 0.22 mL (3.52 mmol) of methyl iodide, 4.4 mL of 10% NaOH (aqueous) and 68 mg (0.21 mmol) of tetra-*n*-butyl-ammonium bromide. Stir the mixture for 5 hours, then separate the layers and dry the organic phase over MgSO₄. Concentrate *in vacuo* to a residue and chromatograph (silica gel, 5% MeOH/CH₂Cl₂ + NH₄OH) to give 169 mg of the product compound. Mass Spec.: MH⁺ = 475

10

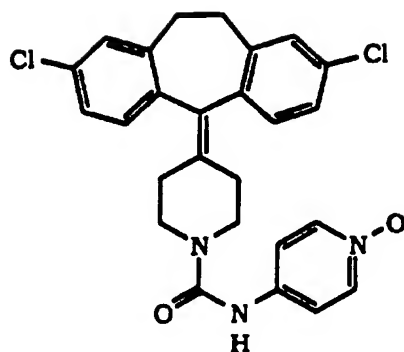
EXAMPLE 422

Combine 0.1 g (0.21 mmol) of the product compound of Example 411-L and 10 mL of CH₂Cl₂, add 0.11 g (0.66 mmol) of MCPBA and stir at ambient temperature for 1 hour. Wash with saturated NaHCO₃ (aqueous), dry over MgSO₄, and concentrate *in vacuo* to give 0.14 gm of the product compound. m.p.=100°-104°C

15

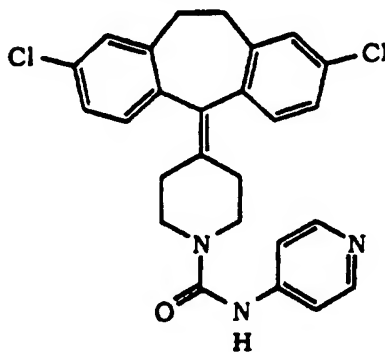
Using the compound of Example 423 and following substantially the same procedure as described for Example 422 the compound:

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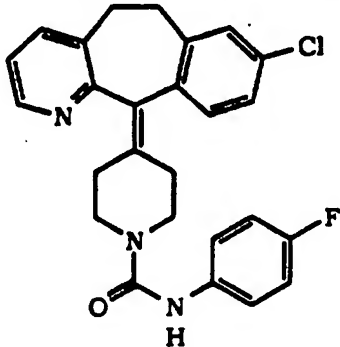
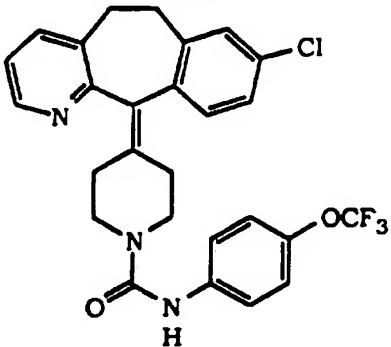
(Example 422-A)

was prepared. Mass Spec.: (FAB) $MH^+ = 480.2$

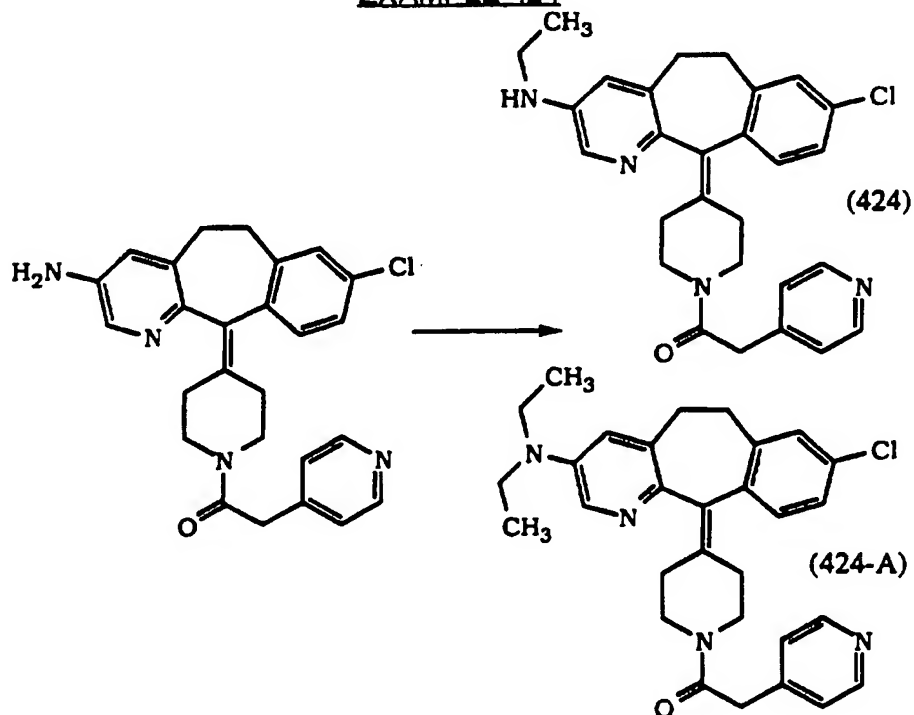
EXAMPLE 423

- 5 Combine 0.4 g (1.22 mmol) of the product compound of Preparative Example 59 and 0.2 g (1.2 mmol) of 4-aminopyridylethylcarbamate and heat to 180°C under a dry N₂ atmosphere for 2 hours. Cool the mixture and crystallize the product by adding EtOAc to give 0.49 g of the product compound. m.p.= 206.4°-207°C; Mass Spec.: (FAB) $MH^+=464.0$
- 10 Using the appropriate ethylcarbamate and the starting compound indicated, the compounds in Table 8 were prepared via substantially the same procedure as described for Example 423:

TABLE 8

Starting Compound	Product Compound	Analytical Data
Preparative Example 1, Step G of WO 95/10516	 Example 423-A	-----
Preparative Example 1, Step G of WO 95/10516	 Example 423-B	-----

EXAMPLE 424



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Combine 1 g of the product of Example 402 and 20 mL of MeOH, cool to -0°C , and adjust to pH = 3 by adding 1 N HCl (aqueous). Add 1.25 mL of CH_3CHO and 1.41 g of NaCNBH_3 , and stir the mixture for 1 hour.

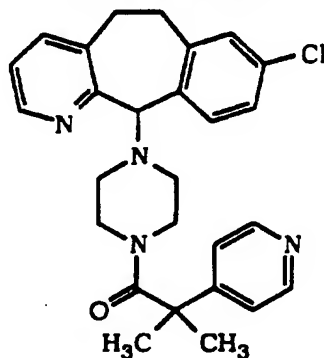
Concentrate *in vacuo* to a residue, extract with 100 mL of CH_2Cl_2 and

5 wash the extract with 100 mL of 10% NaHCO_3 , then with 100 mL of water.

Dry over MgSO_4 , concentrate *in vacuo* to a residue and chromatograph (silica gel, 1.5% (10% NH_4OH in MeOH)/ CH_2Cl_2) to give 0.158 g of the product compound of Example 424 and 0.198 g of the product compound Example 424-A. Mass Spec. (424): $\text{MH}^+ = 474$. Mass Spec. (424-A):

10 $\text{MH}^+ = 502$.

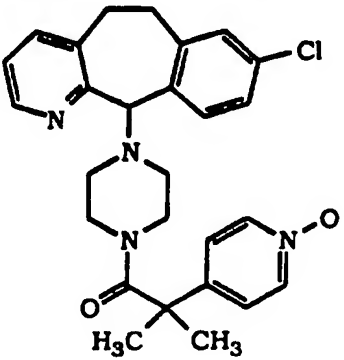
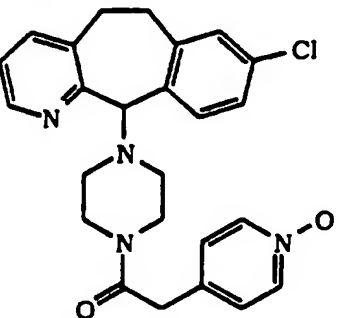
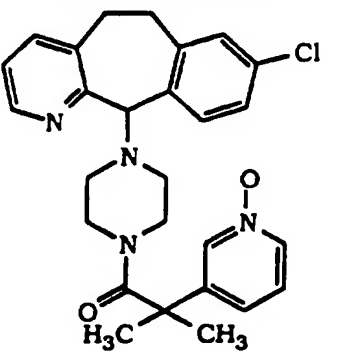
EXAMPLE 425

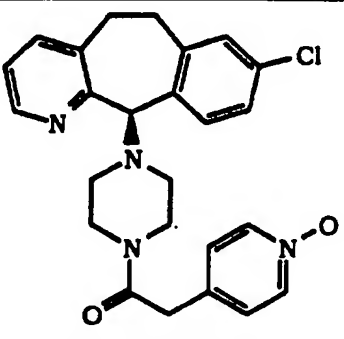
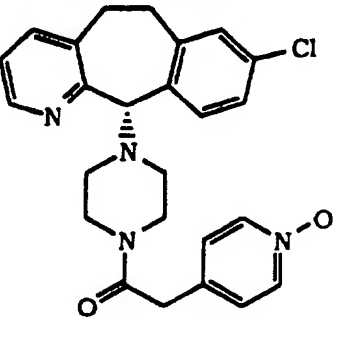
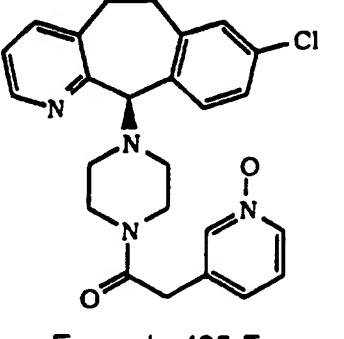
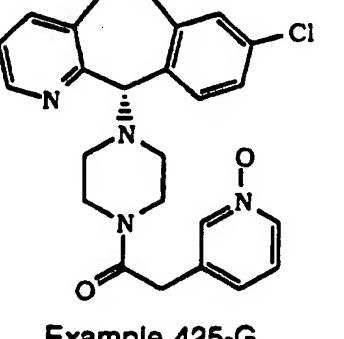


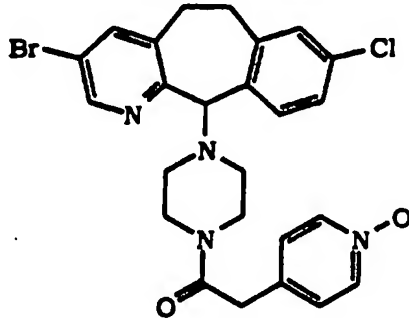
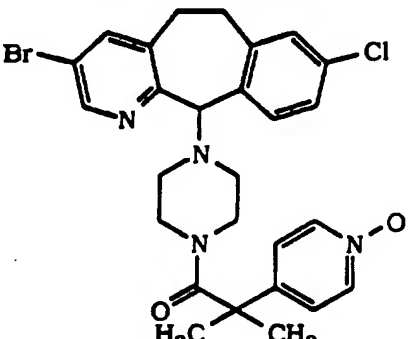
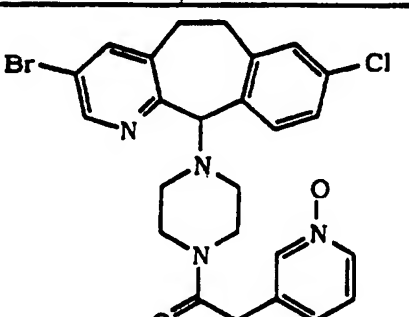
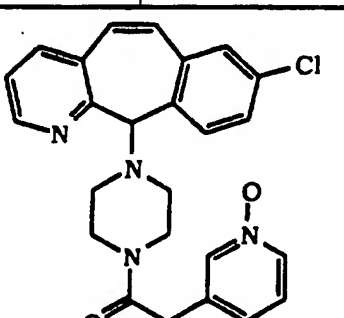
React the products of Preparative Example 7, Step C, of WO 95/10516, and Preparative Example 26, of WO 95/10516, via substantially
15 the same procedure as described for Example 75, of WO 95/10516, to give the title compound. Mass Spec.: $\text{MH}^+ = 461.35$

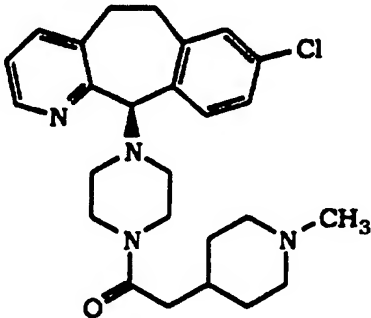
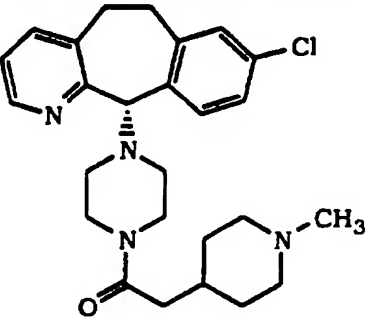
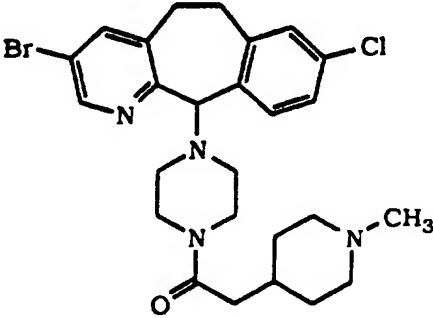
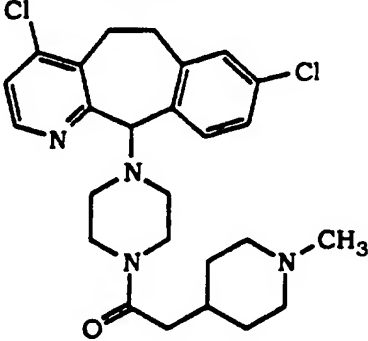
Using the appropriate carboxylic acid and the starting compound indicated, the compounds in Table 9 were prepared via substantially the same procedure as described for Example 425:

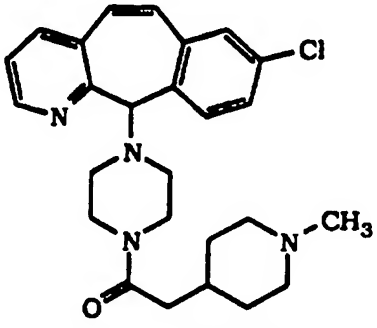
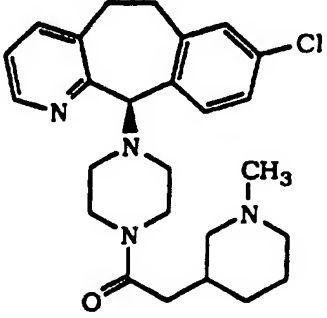
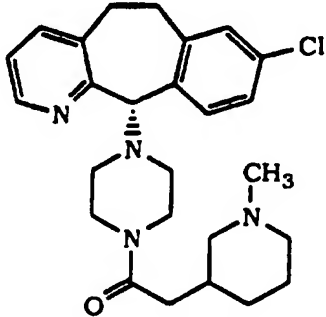
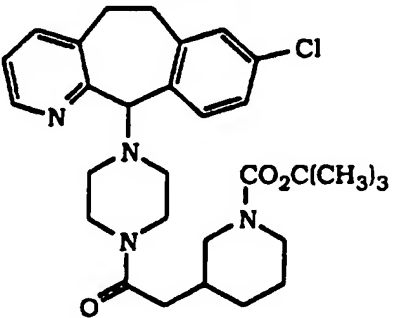
TABLE 9

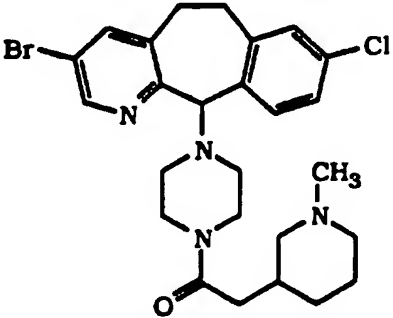
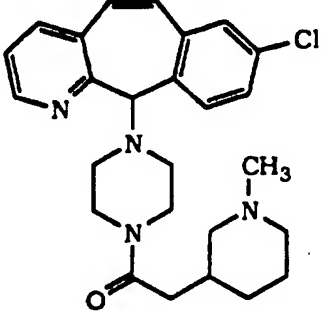
Starting Compound	Product Compound	Analytical Data
Preparative Example 7 of WO 95/10516	 Example 425-A	Mass Spec.: MH ⁺ = 477.2
Preparative Example 7 of WO 95/10516	 Example 425-B	Mass Spec.: MH ⁺ = 449.3
Preparative Example 7 of WO 95/10516	 Example 425-C	Mass Spec.: MH ⁺ = 477.2

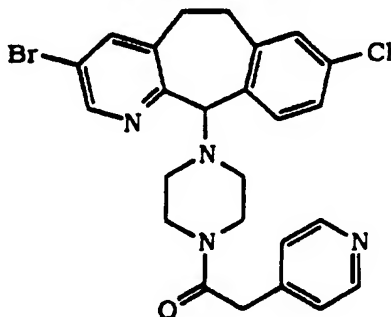
Preparative Example 19 of WO 95/10516 R(+)-isomer	 Example 425-D	Mass Spec.: MH ⁺ = 449.2
Preparative Example 19 of WO 95/10516 S(-)-isomer	 Example 425-E	Mass Spec.: MH ⁺ = 449.2
Preparative Example 19 of WO 95/10516 R(+)-isomer	 Example 425-F	Mass Spec.: MH ⁺ = 449.3
Preparative Example 19 of WO 95/10516 S(-)-isomer	 Example 425-G	Mass Spec.: MH ⁺ = 449.3

Preparative Example 40 of WO 95/10516	 Example 425-H	Mass Spec.: MH ⁺ = 527.0
Preparative Example 40 of WO 95/10516	 Example 425-J	Mass Spec.: MH ⁺ = 555.3
Preparative Example 40 of WO 95/10516	 Example 425-K	Mass Spec.: MH ⁺ = 527.1
Preparative Example 38 of WO 95/10516	 Example 425-L	Mass Spec.: MH ⁺ = 447.2

Preparative Example 19 of WO 95/10516 R(+)-isomer	 Example 425-M	Mass Spec.: MH ⁺ = 453
Preparative Example 19 of WO 95/10516 S(-)-isomer	 Example 425-N	Mass Spec.: MH ⁺ = 453
Preparative Example 40 of WO 95/10516	 Example 425-O	Mass Spec.: MH ⁺ = 531.25
Preparative Example 41 of WO 95/10516	 Example 425-P	Mass Spec.: MH ⁺ = 487.35

Preparative Example 38 of WO 95/10516	 Example 425-Q	Mass Spec.: MH ⁺ = 451.35
Preparative Example 19 of WO 95/10516 R(+)-isomer	 Example 425-R	Mass Spec.: MH ⁺ = 453.35
Preparative Example 19 of WO 95/10516 S(-)-isomer	 Example 425-S	Mass Spec.: MH ⁺ = 453.35
Preparative Example 7 Step C of WO 95/10516	 Example 425-T	Mass Spec.: MH ⁺ = 539.45

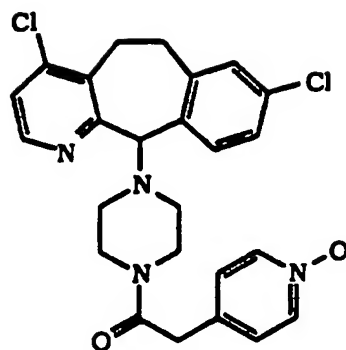
<p>Preparative Example 40 of WO 95/10516</p>	 <p>Example 425-U</p>	<p>Mass Spec.: $MH^+ = 531.35$</p>
<p>Preparative Example 38 of WO 95/10516</p>	 <p>Example 425-V</p>	<p>Mass Spec.: $MH^+ = 451.4$</p>

EXAMPLE 426

React the product of Preparative Example 40, of WO 95/10516, and 3-pyridylacetic acid via substantially the same procedure as described for
5 Example 351, of WO 95/10516, to give the title compound. Mass Spec.: $MH^+ = 511$

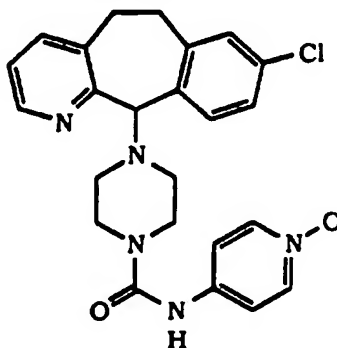
Using the appropriate carboxylic acid and the compound of Preparative Example 41 of WO 95/10516, and following substantially the same procedure as described for Example 426, the compound:

- 99 -



(Example 426-A)

was prepared. Mass Spec.: $MH^+ = 483.2$

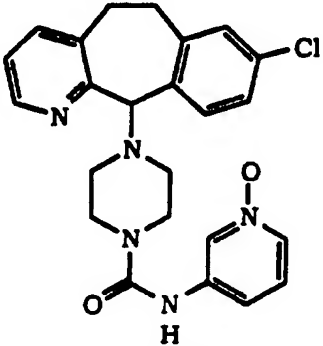
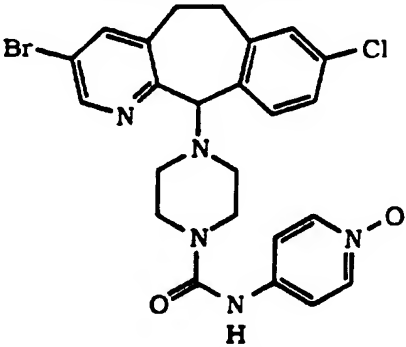
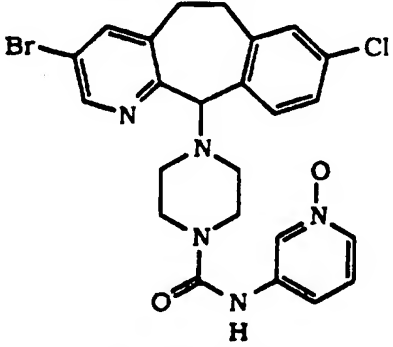
EXAMPLE 427

- 5 Combine 0.288 g (1.76 mmol) of the product of Preparative Example 63 and 25 mL of anhydrous toluene, heated at (110°C) for 0.5 hours, then cool to 25°C. Add a solution of 0.1 g (0.293 mmol) of the product of Preparative Example 7, Step C, of WO 95/10516, in 1.5 mL of anhydrous toluene, and stir at 25°C under an argon atmosphere for 112
- 10 hours. Concentrate *in vacuo* to a residue and chromatograph (silica gel, 3%-4% (10% NH_4OH in MeOH)/ CH_2Cl_2) to give 0.065 g of the title compound. Mass Spec.: $MH^+ = 450.3$

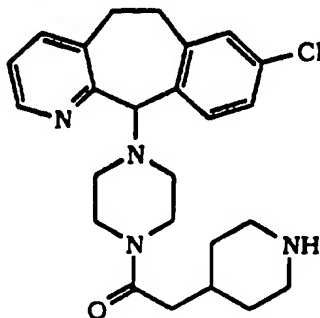
 Using the appropriate azide and the starting compound indicated, the compounds in Table 10 were prepared via substantially the same

15 procedure as described for Example 427:

TABLE 10

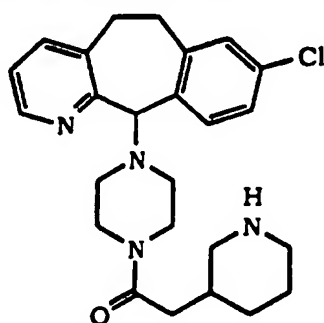
Starting Compound	Product Compound	Analytical Data
Preparative Example 7, Step C of WO 95/10516	 Example 427-A	Mass Spec.: MH ⁺ = 450.1
Preparative Example 40 of WO 95/10516	 Example 427-B	Mass Spec.: MH ⁺ = 528.1
Preparative Example 40 of WO 95/10516	 Example 427-C	Mass Spec.: MH ⁺ = 528.1

EXAMPLE 428



Combine 14.73 g (27.3 mmol) of the compound from Example 193, of WO 95/10516, and 125 mL of anhydrous MeOH, and add (in portions) 300 mL of a 10% solution of concentrated H₂SO₄ in dioxane. Stir the mixture at 25°C for 2 hours, then pour into water and adjust to pH = 13 with 50% NaOH (aqueous). Extract with CH₂Cl₂, wash the extract with water and dry over MgSO₄. Concentrate *in vacuo* to a residue and chromatograph (silica gel, 10% (10% NH₄OH in MeOH)/CH₂Cl₂) to give 8.9 g of the title compound. Mass Spec.: MH⁺ = 539

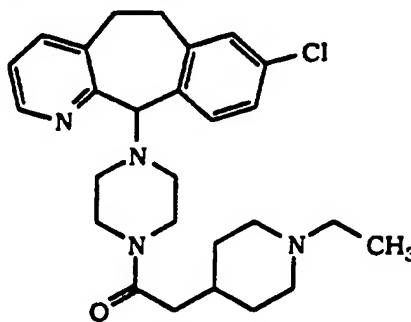
Using the compound of Example 425-T, and following substantially the same procedure as described for Example 428, the compound:



(Example 428-A)

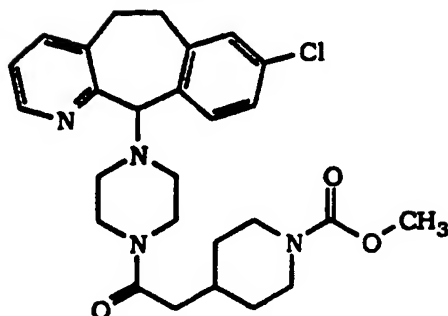
was prepared. Mass Spec.: MH⁺ = 439.45

EXAMPLE 429

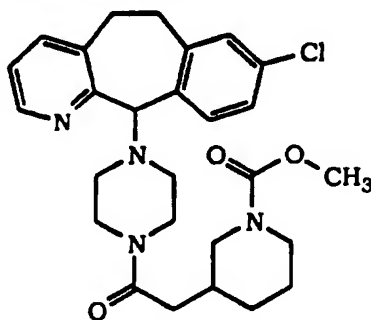


Combine 0.5 g (1.14 mmol) of the compound of Example 428 and 10 mL of 0.6 N HCl in CH₂Cl₂, stir for 10 minutes and concentrate *in vacuo* to a residue. Add 20 mL of anhydrous MeOH, then add 0.2006 g (4.56 mmol) of CH₃CHO, 0.0859 g (1.36 mmol) NaCNBH₃ and 0.5 g of 3A molecular sieves, and heat at 40°C for 115 hours. Filter the mixture, wash the sieves with MeOH and concentrate the combined filtrates *in vacuo* to a residue. Dissolve the residue in CH₂Cl₂ and wash with saturated NaHCO₃ (aqueous), then water and dry over MgSO₄. Concentrate *in vacuo* to a residue and chromatograph (silica gel, 8% (10% NH₄OH in MeOH)/CH₂Cl₂) to give the title compound. Mass Spec.: MH⁺ = 467.3

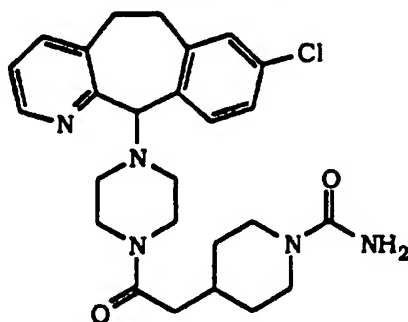
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EXAMPLE 430

- Combine 0.5 g (1.14 mmol) of the compound of Example 428 and 5 mL of anhydrous THF, add 0.1076 g (1.14 mmol) ClCO_2CH_3 , and stir at 25°C for 1 hour. Concentrate *in vacuo* to a residue, add CH_2Cl_2 and wash with saturated NaHCO_3 (aqueous), then water. Dry the organic phase over MgSO_4 , concentrate *in vacuo* to a residue and chromatograph (silica gel, 1.5% (10% NH_4OH in MeOH)/ CH_2Cl_2) to give 0.4213 g of the title compound. Mass Spec.: $\text{MH}^+ = 497.35$
- Using the compound of Example 428-A, and following substantially the same procedure as described for Example 430, the compound:



(Example 430-A)

was prepared. Mass Spec.: $\text{MH}^+ = 497.35$ **EXAMPLE 431**

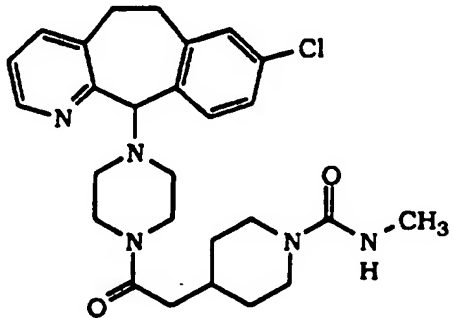
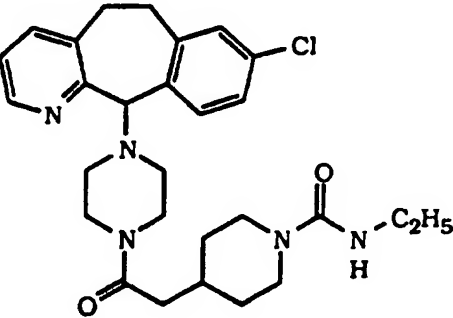
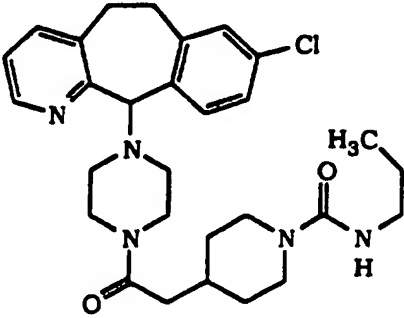
15

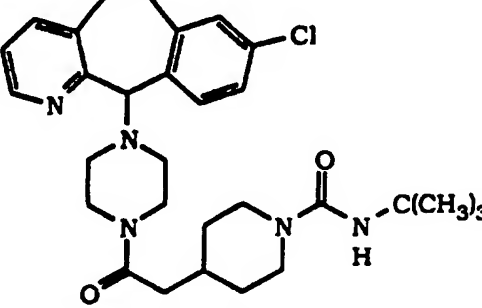
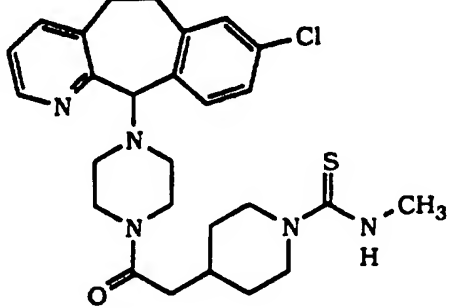
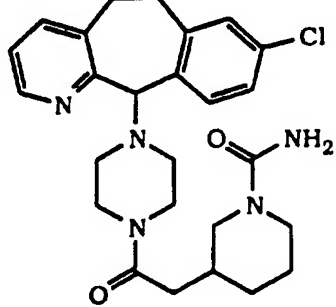
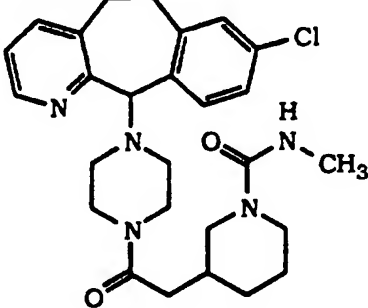
Combine 0.5 g (1.14 mmol) of the compound of Example 428 and 5 mL of anhydrous CH_2Cl_2 , add 0.2624 g (2.28 mmol) of trimethylsilylisocyanate and stir under argon at 25°C for 22 hours. Add

- 0.1312 g (1.14 mmol) of trimethylsilylisocyanate and stir for 8 hours, then dilute with CH_2Cl_2 and wash with saturated NaHCO_3 (aqueous), then water. Dry over MgSO_4 , concentrate *in vacuo* to a residue and chromatograph (silica gel, 5% (10% NH_4OH in MeOH)/ CH_2Cl_2) to give
- 5 0.3878 g of the title compound. Mass Spec.: $\text{MH}^+ = 482.2$

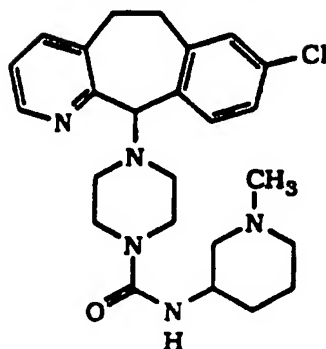
Using the isocyanate (or isothiocyanate) and starting compound indicated, the compounds in Table 11 were prepared via substantially the same procedure as described for Example 431:

TABLE 11

Starting Compound	Product Compound	Analytical Data
CH_3NCO and Example 428	 <p>Example 431-A</p>	Mass Spec.: $\text{MH}^+ = 496.45$
$\text{CH}_3\text{CH}_2\text{NCO}$ and Example 428	 <p>Example 431-B</p>	Mass Spec.: $\text{MH}^+ = 510.35$
$\text{CH}_3(\text{CH}_2)_2\text{NCO}$ and Example 428	 <p>Example 431-C</p>	Mass Spec.: $\text{MH}^+ = 524.35$

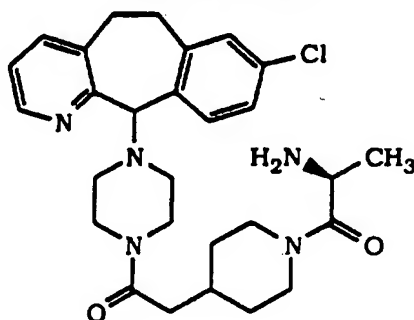
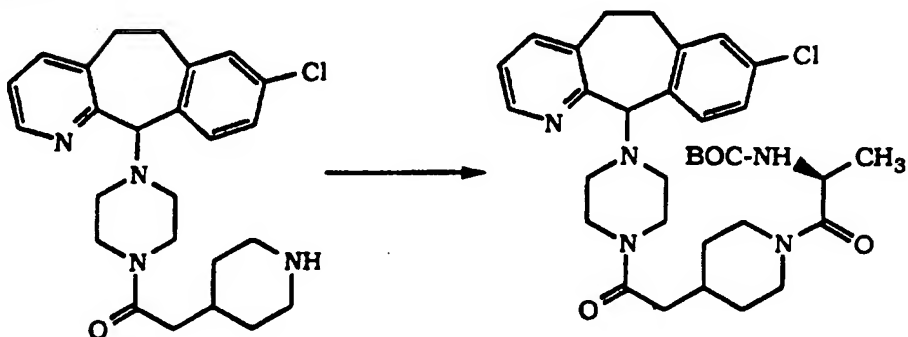
<p>(CH₃)₃C-NCO and Example 428</p>	 <p>Example 431-D</p>	<p>Mass Spec.: MH⁺ = 538.35</p>
<p>CH₃NCS and Example 428</p>	 <p>Example 431-E</p>	<p>Mass Spec.: MH⁺ = 512.25</p>
<p>(CH₃)₃Si-NCO and Example 428-A</p>	 <p>Example 431-F</p>	<p>Mass Spec.: MH⁺ = 482.3</p>
<p>CH₃NCO and Example 428-A</p>	 <p>Example 431-G</p>	<p>Mass Spec.: MH⁺ = 496.35</p>

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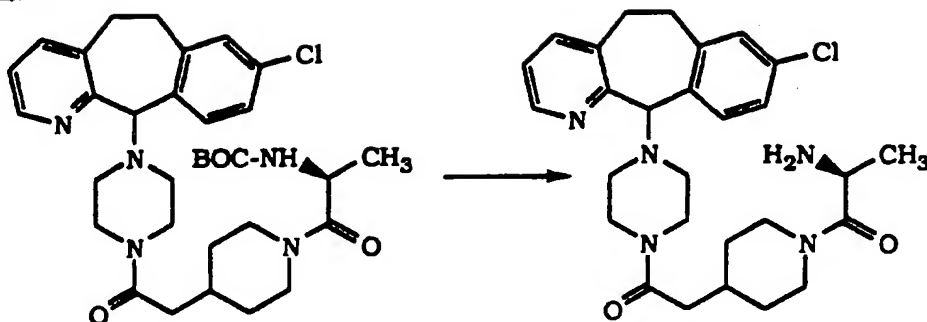
EXAMPLE 432

Combine 0.5 g (1.6 mmol) of the compound of Preparative Example 7, of WO 95/10516, and 1.098 g (6.4 mmol) of the compound from
 5 Preparative Example 65 and heat in a sealed vessel at 160°C for 17 hours. Cool the mixture, add CH₂Cl₂, wash with water and dry the organic phase over MgSO₄. Concentrate *in vacuo* to a residue and chromatograph (silica gel, 1.5% (10% NH₄OH in MeOH)/CH₂Cl₂) to give 0.0364 g of the title compound. Mass Spec.: MH⁺ = 454.25

10

EXAMPLE 433**Step A:**

React 0.5 g (1.59 mmol) of the compound of Example 428 and
 15 0.3232 g (2.39 mmol) of N-(tert-butoxycarbonyl)-L-alanine (0.3232 grams) (2.39 mmoles) via essentially the same conditions as described in Example 425 to give the product compound.

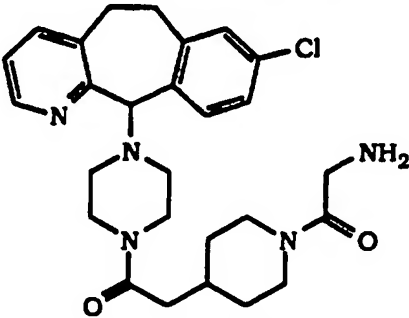
Step B:

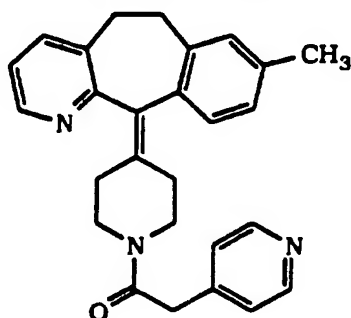
Combine the product of Step A, 5 mL of MeOH and 10 mL of 10% concentrated H_2SO_4 in dioxane and stir at 25°C for 2 hours. Neutralize with Biorad AG1X8 (OH^-) ion exchange resin, filter, wash the resin with 1:1 MeOH/water and concentrate the filtrate to a residue. Chromatograph the residue (silica gel, 8% (10% NH_4OH in MeOH)/ CH_2Cl_2) to give the title compound. Mass Spec.: $\text{MH}^+ = 510.35$

Using the appropriate BOC-amino acid and the starting compound indicated, the compounds in table 12 were prepared via substantially the same procedure as described for Example 433:

TABLE 12

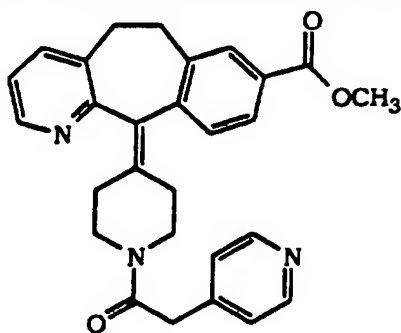
Starting Compound	Product Compound	Analytical Data
BOC-L-serine and Example 428	 Example 433-A	Mass Spec.: $\text{MH}^+ = 526.2$
BOC-L-methionine and Example 428	 Example 433-B	Mass Spec.: $\text{MH}^+ = 570.3$

BOC-glycine and Example 428	 <p>Example 433-C</p>	Mass Spec.: MH ⁺ = 496.35
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EXAMPLE 434

React the product of Preparative Example 67 with 4-pyridylacetic acid via essentially the same procedure as described for Example 411 to give the title compound. Mass Spec.: MH⁺ = 410

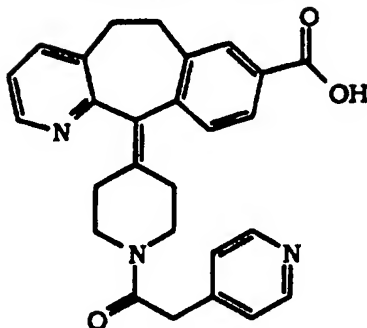
Using the appropriate carboxylic acid and the compound of Preparative Example 68, and following substantially the same procedure as described for Example 434, the compound:



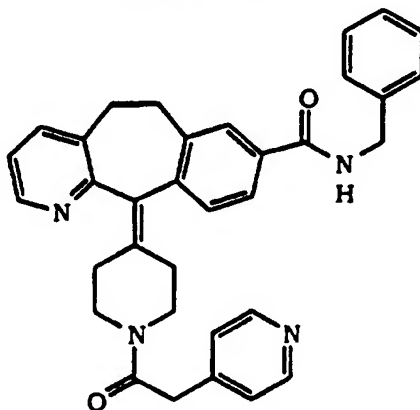
(Example 434-A)

was prepared. m.p. = 68.6°-70.3°C, Mass Spec.: MH⁺=454.

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EXAMPLE 435

5 Dissolve 3.04 g (6.7 mmol) of the compound of Example 434-A in 100 mL of MeOH. Add 100 mL of a 12% KOH (aqueous) and stir for one hour at 25°C. Remove the MeOH under vacuum, neutralize to pH 7 with 12 N HCl and concentrate *in vacuo* to a residue. Dry under vacuum and triturate with 10 mL of EtOH, then filter, concentrate the filtrate *in vacuo* to give the title compound. m.p. = 238°-240° C; Mass Spec.: MH⁺ = 440

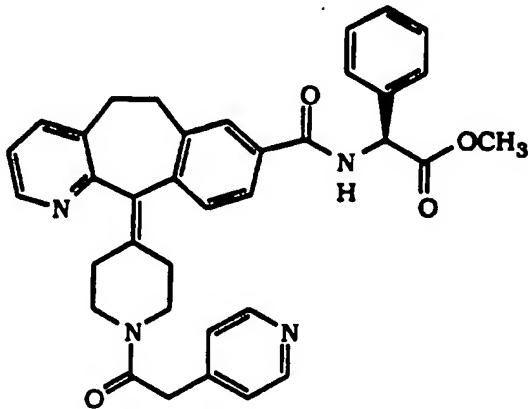
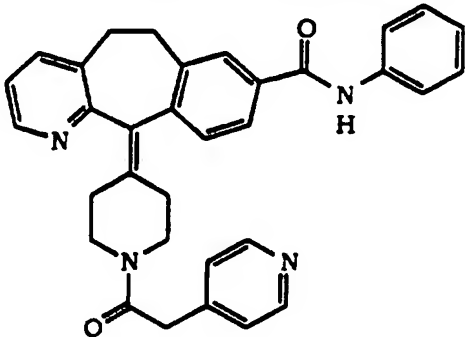
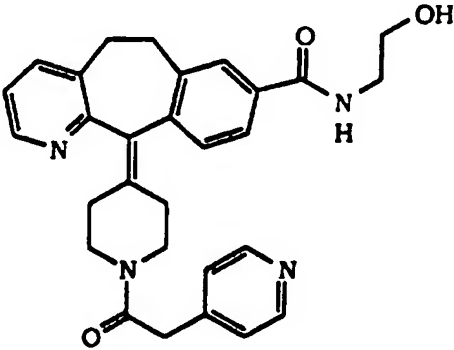
EXAMPLE 436

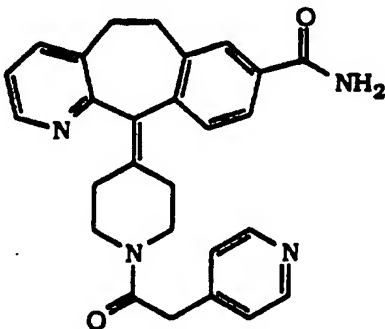
10

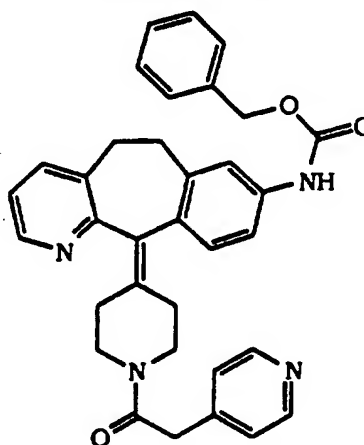
Dissolve 0.5 g (1.14 mmol) of the product of Example 435 in 25 mL of DMF, add 0.122 g (1.14 mmol) of benzylamine, 0.33 g (1.7 mmol) of DEC, 0.15 g (1.1 mmol) of HOBT, and 0.23 g (2.27 mmol) of N-methylmorpholine, and stir at 25°C, under nitrogen for 18 hours. Concentrate *in vacuo* to a residue, add 20 mL of water and extract with 50 mL of EtOAc. Dry the organic layer over MgSO₄ and concentrate *in vacuo* to a residue. Chromatograph (silica gel, 98% CH₂Cl₂/MeOH + NH₄OH) to give the product compound. m.p.=118°-120°C; Mass Spec.: MH⁺=529

15 Using the appropriate amine and the starting compound indicated, 20 the compounds in Table 13 were prepared via substantially the same procedure as described for Example 436:

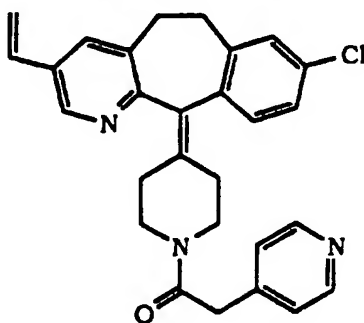
TABLE 13

Starting Compound	Product Compound	Analytical Data
S-phenylalanine methyl ester and Example 435	 <p>Example 436-A</p>	m.p. = 116.9°-118.4°C Mass Spec.: MH ⁺ = 622
aniline and Example 435	 <p>Example 436-B</p>	m.p. = 137.8°-139.9°C Mass Spec.: MH ⁺ = 516
ethanolamine and Example 435	 <p>Example 436-C</p>	m.p. = 130.9°-132.5°C Mass Spec.: MH ⁺ = 482

<p>NH₄Cl and Example 435</p>	 <p>Example 436-D</p>	<p>m.p. = 133.2°- 133.5°C Mass Spec.: MH⁺ = 439</p>
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EXAMPLE 437

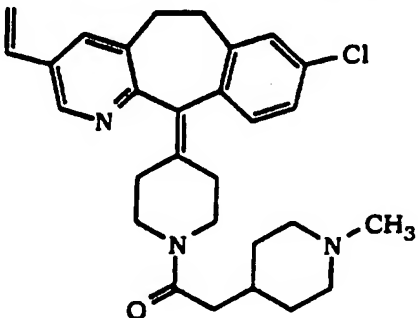
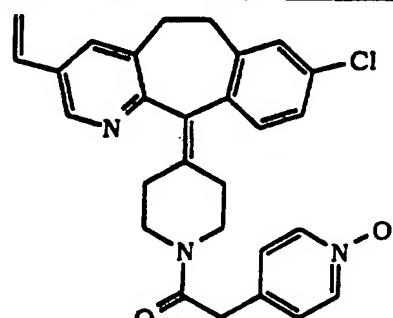
Dissolve 0.18 g (0.41 mmol) of the product of Example 435 in 2 mL of toluene, add 0.12 g (0.43 mmol) of diphenylphosphoryl azide, 0.041 g
5 (0.41 mmol) of Et₃N, and 0.092 g (0.44 mmol) of benzyl alcohol and heat at reflux under nitrogen for 18 hours. Concentrate *in vacuo* to a residue and chromatograph (silica gel 95% CH₂Cl₂/MeOH) to obtain the title compound. m.p. = 132.8°-133.7°C; MH⁺ = 545

EXAMPLE 438

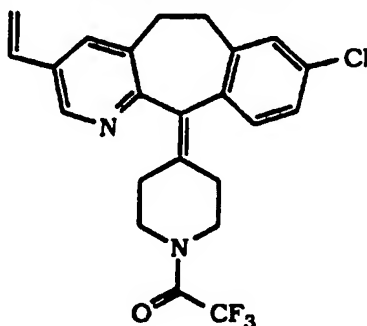
React the product of Preparative Example 70 with 4-pyridylacetic acid via essentially the same procedure as described for Example 411 to give the title compound. Mass Spec.: (FAB) $MH^+ = 456$

- 5 Using the appropriate carboxylic acid and the starting compound indicated, the compounds of Table 14 were prepared via substantially the same procedure as described for Example 438:

TABLE 14

Starting Compound	Product Compound	Analytical Data
Preparative Example 70	 <p>Example 438-A</p>	Mass Spec.: (FAB) $MH^+ = 476$
Preparative Example 70	 <p>Example 438-B</p>	Mass Spec.: (FAB) $MH^+ = 472$

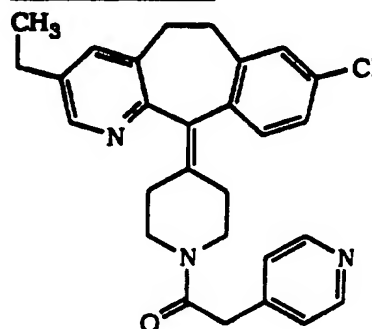
EXAMPLE 439



- 10 Combine 1.7 g (5 mmol) of the product of Preparative Example 70, Step D, and 10 mL of anhydrous pyridine at 0°C under N_2 atmosphere,

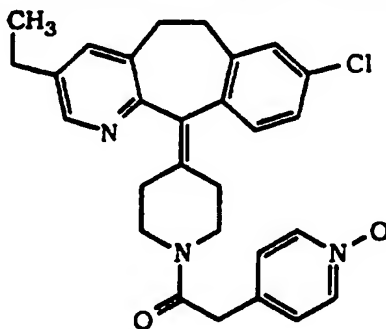
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then slowly add (dropwise) 1 mL (7 mmol) of TFAA and stir at 25°C overnight. Dilute with 100 ml of cold water, extract with CH₂Cl₂ (2 x 75 mL), wash the extracts successfully with 10% CuSO₄ (aqueous) and brine, then dry over MgSO₄. Concentrate *in vacuo* to a residue and chromatograph (silica gel 30%40% EtOAc/hexane) to give 1.75 g of the title compound. Mass Spec.: (FAB) MH⁺ = 433

EXAMPLE 440

Combine 0.07 g (0.154 mmol) of the product of Example 438, 7 mL of EtOH and 12 mg of PtO₂, and hydrogenate at 25°C and atmospheric pressure for 1 hour. Filter, wash with EtOH and concentrate *in vacuo* to give 0.066 g of the title compound. Mass Spec.: (FAB) MH⁺ = 458

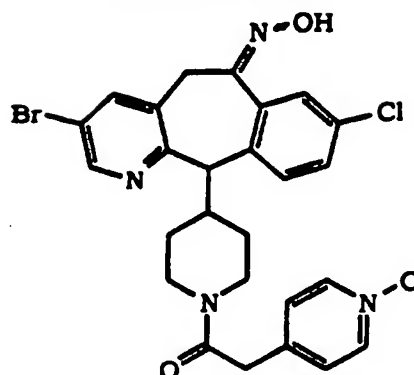
Using the compound of Example 438-B, and following substantially the same procedure as described for Example 440, the compound:



15

(Example 440-A)

was prepared. Mass Spec.: (FAB) MH⁺ = 474

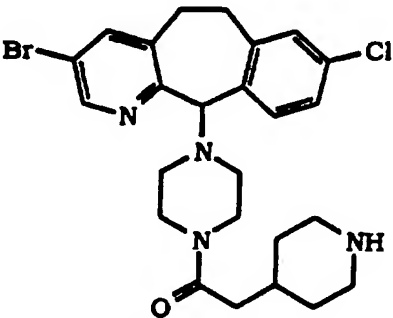
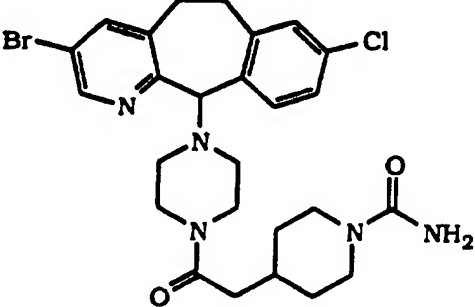
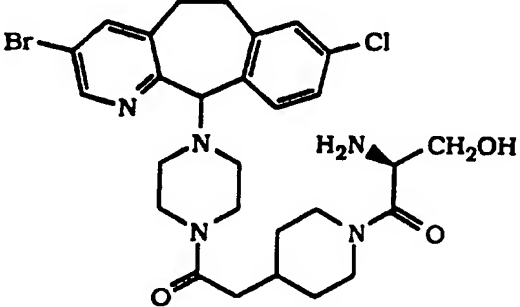
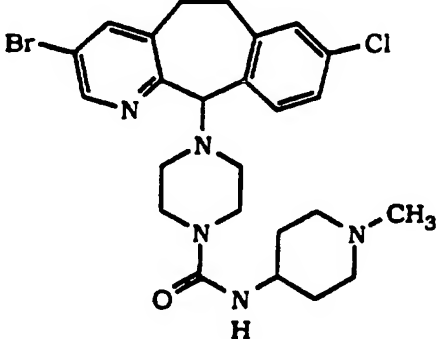
EXAMPLE 441

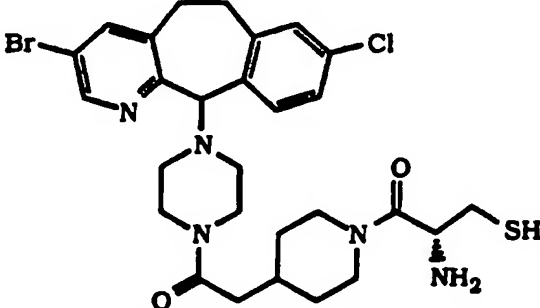
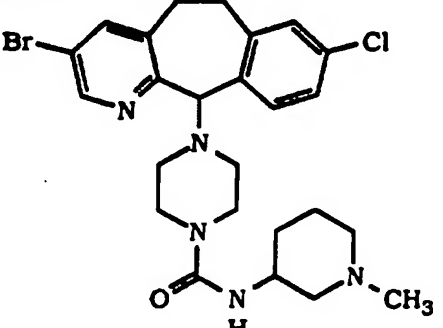
Combine 0.07 g of the compound of Example 410-R, 2 mL of THF, 0.5 mL of water, 10 drops of glacial HOAc, and 0.1 g of powdered Zn, and stir the mixture for 0.5 hours at 25°C. Purify the mixture by preparative thin layer chromatography (Prep TLC), (silica gel, 10% (10% NH₄OH in MeOH)/CH₂Cl₂), to give a total of 68 mg of the crude product. Purify again by Prep TLC), (silica gel, 13% (10% NH₄OH in MeOH)/CH₂Cl₂), to give 33 mg of the product compound. Mass Spec.: MH⁺ = 555

The compounds in Table 15 were prepared using the product of Preparative Example 40, of WO 95/10516, and following substantially the same procedures as described for Examples 183 and 193 of WO 95/10516, and Examples 428, 431, 433-A disclosed above, as appropriate:

TABLE 15

Example No.	Compound	Analytical Data
500		Mass Spec.: MH ⁺ = 619.15

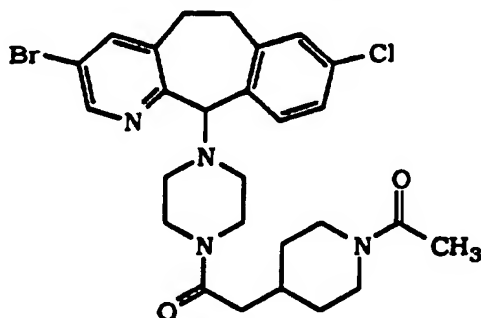
501		Mass Spec.: $MH^+ = 517$
502		Mass Spec.: $MH^+ = 560$
503		Mass Spec.: $MH^+ = 604.2$
504		Mass Spec.: $MH^+ = 532.15$

505		Mass Spec.: $MH^+ = 622.1$
506		Mass Spec.: $MH^+ = 534.3$

Analytical data for Example 505 are: 1H NMR: δ_H (D_2O) 7.35 (1H, aromatic), 7.44 (1H, aromatic), 7.49 (1H, aromatic), 7.93 (1H, aromatic) and 8.58 (1H, aromatic).

- Analytical data for Example 506 are: δ_C ($CDCl_3$) (a) Tricyclic: (i) CH_2 : 30.0, 30.0; (ii) CH : 146.5, 140.7, 132.0, 125.7, 130.0, 78.6; and (iii) C : 119.4, 140.3, 133.6, 135.0, 136.3, 155.4; (b) Piperazine: (i) CH_2 : 43.4, 43.4, 50.8, 50.8; and (c) Piperazine N-substituent: (i) CH_3 : 46.1; (ii) CH_2 : 28.3, 21.4, 55.4; (iii) CH : 45.5; and (iv) C : 156.4.

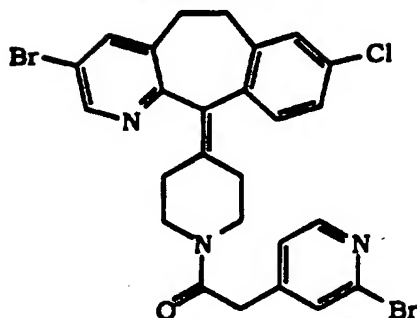
EXAMPLE 507



10

React the compound of Example 501 with an excess of acetic anhydride in MeOH via standard procedures to form the product compound in 91% yield. Mass Spec.: $MH^+ = 559$

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EXAMPLE 508

React the compound of Preparative Example 49 with 4-(2-bromopyridyl)acetic acid via the substantially the same procedure as described for Example 410 to give the product compound. m.p. = 134°-136.1°C; Mass Spec.: MH⁺ = 588

ASSAYS

FPT IC₅₀ (inhibition of farnesyl protein transferase, in vitro enzyme assay), GGPT IC₅₀ (inhibition of geranylgeranyl protein transferase, in vitro enzyme assay), COS Cell IC₅₀ (Cell-Based Assay) and Cell Mat Assay were determined by the methods disclosed in WO 95/10516. Results of these assays are given in Tables 16-19.

TABLE 16 - FPT INHIBITION

EXAMPLE	FPT IC ₅₀ (μM)	EXAMPLE	FPT IC ₅₀ (μM)
400 (5.210)	0.01-10	401 (5.209)	0.01-10
400-B (5.203)	0.01-10	400-C (5.200)	0.01-10
400-D (5.217)	0.01-10	400-E (5.208)	0.01-10
400-F (5.201)	0.01-10	400-G (5.204)	0.01-10
400-H (5.220)	0.01-10	400-J (5.212)	0.01-10
400-K (5.218)	0.01-10	400-L (5.206)	0.01-10
411	0.01-10	411-A	0.01-10
411-B	0.01-10	402-A	0.01-10
411-D	0.01-10	411-E	0.01-10
411-F	0.01-10	411-G	0.01-10
411-L	0.01-10	402	0.01-10
405	0.01-10	406	0.01-10
413	0.01-10	414-A	0.01-10
414	0.01-10	417	0.01-10
418	0.01-10	417-A	0.01-10
417-B	0.01-10	419	0.01-10

420	0.01-10	422	0.01-10
423	0.01-10	422-A	0.01-10
411-N	0.01-10	411-M	0.01-10
411-R	0.01-10	411-S	0.01-10
411-P	0.01-10	411-Q	10-100
411-O	0.01-10	411-X	0.01-10
411-V	0.01-10	411-T	0.01-10
411-W	0.01-10	411-U	0.01-10
425	0.01-10	425-B	0.01-10
425-A	0.01-10	425-C	0.01-10
425-E	0.01-10	425-D	0.01-10
425-G	0.01-10	425-F	0.01-10
426 (5.207)	0.01-10	425-H (5.202)	0.01-10
425-J	0.01-10	425-K	0.01-10
425-L	0.01-10	426-A	0.01-10
427	0.01-10	427-A	0.01-10
425-N	0.01-10	428	0.01-10
429	0.01-10	425-M	0.01-10
431	0.01-10	431-C	0.01-10
431-B	0.01-10	431-D	0.01-10
431-A	0.01-10	430	0.01-10
431-E	0.01-10	425-O (5.216)	0.01-10
425-P	0.01-10	425-Q	0.01-10
425-S	0.01-10	425-R	0.01-10
428-A	0.01-10	431-F	0.01-10
430-A	0.01-10	431-G	0.01-10
425-T	10-100	425-U (5.211)	0.01-10
425-V	0.01-10	434	0.01-10
434-A	0.01-10	435	0.01-10
437	10-100	411-Z	0.01-10
427-B	0.01-10	427-C	0.01-10
432	0.01-10	415	0.01-10
411-C	0.01-10	400-M	0.01-10
411-DD	0.01-10	411-EE	10-100
411-FF	0.01-10	----	----

410-W	0.01-10	410-G	0.01-10
410-H	0.01-10	410-J	0.01-10
412	0.01-10	410-L	0.01-10
403	10-100	404	0.01-10
401-A	0.01-10	400-A	0.01-10
412	0.01-10	416	0.01-10
410-M	10-100	424	0.01-10
424-A	10-100	433	0.01-10
433-A	0.01-10	433-B	0.01-10
433-C	0.01-10	436	10-100
436-A	10-100	436-B	10-100
436-C	10-100	436-D	0.01-10
410-S	10-100	410-T	0.01-10
410-U	0.01-10	410-V	0.01-10
505	0.01-10	506	0.01-10

TABLE 17

COMPARISON OF FPT INHIBITION AND GGPT INHIBITION

EXAMPLE	ENZYME INHIBITION FPT IC ₅₀ μ M	ENZYME INHIBITION GGPT IC ₅₀ μ M
400-D	0.01-10	>38
400-C	0.01-10	>38
400-B	0.01-10	>38
400-E	0.01-10	30% @ 38 μ M
400-F	0.01-10	0% @ 36 μ M
400-G	0.01-10	>39
400-H	0.01-10	0% @ 36 μ M
400-J	0.01-10	6% @ 36 μ M
400-K	0.01-10	0% @ 37 μ M
400	0.01-10	29% @ 36 μ M
401	0.01-10	7% @ 34 μ M
413	0.01-10	>35
417-B	0.01-10	15% @ 32 μ M
419	0.01-10	0% @ 41 μ M
411-W	0.01-10	3% @ 42 μ M
426	0.01-10	>39

425-H	0.01-10	>38
425-O	0.01-10	>38
425-U	0.01-10	>38
400-L	0.01-10	38
410-G	0.01-10	32% @ 33 μ M

TABLE 18 - ACTIVITY IN COS CELLS

Example	Inhibition of Ras Processing IC ₅₀ (μ M)	Example	Inhibition of Ras Processing IC ₅₀ (μ M)
411	0.01-10	411-A	0.01-10
411-B	0.01-10	411-D	0.01-10
400-D	0.01-10	400-C	0.01-10
402	10-100	411-G	0.01-10
400-G	0.01-10	400-H	0.01-10
400-K	0.01-10	411-B	0.01-10
400-D	0.01-10	400-C	0.01-10
400-G	0.01-10	413	0.01-10
417	0.01-10	418	10-100
425-E	0.01-10	426	0.01-10
425-H	0.01-10	425-J	0.01-10
425-K	0.01-10	426-A	0.01-10
425-O	0.01-10	425-P	0.01-10
425-U	0.01-10	434	0.01-10
400-L	0.01-10	410-G	0.01-10

TABLE 19

INHIBITION OF TUMOR CELL GROWTH - MAT ASSAY

Example	Tumor IC ₅₀ (μ M)	Normal IC ₅₀ (μ M)	Example	Tumor IC ₅₀ (μ M)	Normal IC ₅₀ (μ M)
411-A	1.6	> 25	411	18	> 25
411-B	6.25	>25	402-A	3.1	>25
411-D	8	>25	411-E	>25	>25
400-D	4	>25	400-C	<1.6	>25
402	18	>25	400-B	<1.6	6.25
411-G	6.25 4	>25 >12.5	400-E	<1.6	18

400-F	<1.6	>25	405	12.5	>25
400-G	1.6	>25	400	1.6	>25
401	<1.6	>25	411-B	6.25	>25
402-A	3.1	>25	400-D	4	>25
400-C	<1.6	>25	400-B	<1.6	>25
400-G	1.6	>25	413	>6.25	10
417	10	18	418	25	>25
417-B	<1.6	>25	425	12.5	>25
425-B	12.5	>25	425-E	1.6	>25
426	3.1	25	425-H	<1.6	>25
	<0.8	>12.5			
425-J	3.1	>25	425-K	6.25	>25
426-A	6.25	>25	428	12.5	18
425-O	3.1	6.25	425-P	>3.1	3.1
	<0.8	6.25			
425-U	6.25	10	400-L	<1.6	>25
				<0.8	>12.5

RESULTS:**1. Enzymology:**

The data demonstrate that the compounds of the invention are inhibitors of Ras-CVLS farnesylation by partially purified rat brain farnesyl protein transferase (FPT). The data also show that there are compounds of the invention which can be considered as potent ($IC_{50} < 10 \mu M$) inhibitors of Ras-CVLS farnesylation by partially purified rat brain FPT.

The data also demonstrate that compounds of the invention are poorer inhibitors of geranylgeranyl protein transferase (GGPT) assayed using Ras-CVLL as isoprenoid acceptor. Generally, the compounds of the invention are inactive or weakly active as geranylgeranyl transferase inhibitors at $20 \mu g/mL$. This selectivity is important for the therapeutic potential of the compounds used in the methods of this invention, and increases the potential that the compounds will have selective growth inhibitory properties against Ras-transformed cells.

2. Cell-Based: COS Cell Assay

Western blot analysis of the Ras protein expressed in Ras-transfected COS cells following treatment with the tricyclic farnesyl protein transferase inhibitors of this invention indicated that they inhibit Ras-CVLS processing, causing accumulation of unprocessed Ras

These results provide evidence for specific inhibition of farnesyl protein transferase, but not geranylgeranyl transferase I, by compounds of this invention in intact cells and indicate their potential to block cellular transformation by activated Ras oncogenes.

5 3. Cell-Based: Cell Mat Assay

Tricyclic farnesyl protein transferase inhibitors of this invention also inhibited the growth of Ras-transformed tumor cells in the Mat assay without displaying cytotoxic activity against the normal monolayer.

In Vivo Anti-Tumor Studies:

10 Tumor cells (5×10^5 to 8×10^6) of DLD-1 (human colon carcinoma cells, ATCC # CCL 221), and PT-24 (mouse fibroblast cell line transfected with human H-ras), are innoculated subcutaneously into the flank of 5-6 week old athymic nu/nu female mice. Tumor bearing animals are selected and randomized when the tumors are established. Animals are treated
15 with vehicle only or with a compound of the present invention in vehicle four times a day (QID) for 7 days per week for 4 weeks. The percent inhibition of tumor growth relative to vehicle controls is determined by tumor measurements. The results are reported in Table 20.

TABLE 20

IN VIVO ANTI-TUMOR STUDIES

20

EXAMPLE	EXPERIMENT NO.	CELL LINE	DOSE mg/kg (P.O.)	AVERAGE % TUMOR INHIBITION
400-C	1	PT-24	50	99.7
	2	PT-24	10	43.6
	3	DLD-1	50	31
	4	DLD-1	10	21
425-H	1	PT-24	50	95.1
	2	PT-24	10	68.7
	3	DLD-1	50	42
	4	DLD-1	10	37
400-F	1	PT-24	50	78.3
	2	PT-24	10	31.8
400-Q	1	DLD-1	50	70
	2	DLD-1	10	52
	3	DLD-1	50	39
	4	DLD-1	10	21

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The
5 powders and tablets may be comprised of from about 5 to about 70 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar, lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration.

10 For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

15 Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection.

Liquid form preparations may also include solutions for intranasal administration.

20 Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or
25 parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal
30 patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing
35 appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 0.1 mg to 1000 mg, more preferably from about 1 mg. to 300 mg, according to the particular application.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

The amount and frequency of administration of the compounds of the invention and the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended dosage regimen is oral administration of from 10 mg to 2000 mg/day preferably 10 to 1000 mg/day, in two to four divided doses to block tumor growth. The compounds are non-toxic when administered within this dosage range.

The following are examples of pharmaceutical dosage forms which contain a compound of the invention. The scope of the invention in its pharmaceutical composition aspect is not to be limited by the examples provided.

Pharmaceutical Dosage Form Examples

EXAMPLE A

Tablets

No.	Ingredients	mg/tablet	mg/tablet
1.	Active compound	100	500
2.	Lactose USP	122	113
3.	Corn Starch, Food Grade, as a 10% paste in Purified Water	30	40
4.	Corn Starch, Food Grade	45	40
5.	Magnesium Stearate	__3	__7
Total		300	700

Method of Manufacture

Mix Item Nos. 1 and 2 in a suitable mixer for 10–15 minutes.

Granulate the mixture with Item No. 3. Mill the damp granules through a coarse screen (e.g., 1/4", 0.63 cm) if necessary. Dry the damp granules.

- 5 Screen the dried granules if necessary and mix with Item No. 4 and mix for 10–15 minutes. Add Item No. 5 and mix for 1–3 minutes. Compress the mixture to appropriate size and weigh on a suitable tablet machine.

EXAMPLE B**Capsules**

No.	Ingredient	mg/capsule	mg/capsule
1.	Active compound	100	500
2.	Lactose USP	106	123
3.	Corn Starch, Food Grade	40	70
4.	Magnesium Stearate NF	<u>7</u>	<u>7</u>
Total		253	700

10 **Method of Manufacture**

Mix Item Nos. 1, 2 and 3 in a suitable blender for 10-15 minutes.

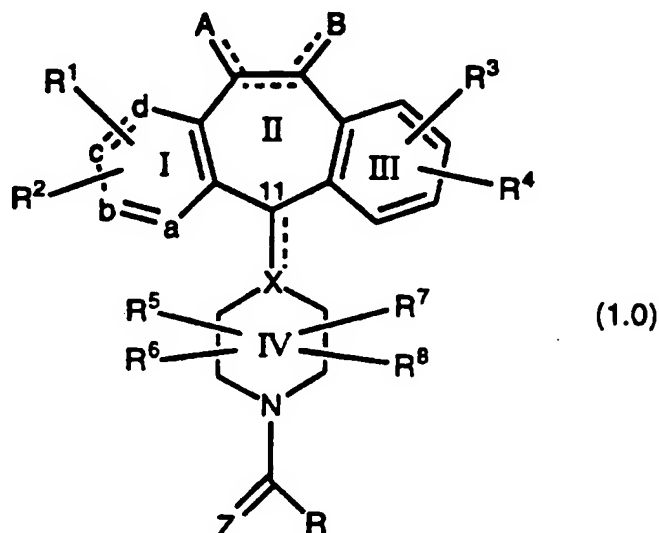
Add Item No. 4 and mix for 1-3 minutes. Fill the mixture into suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

- 15 While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

WHAT IS CLAIMED IS:

1. A method for inhibiting the abnormal growth of cells comprising administering an effective amount of a compound of Formula

5 1.0:

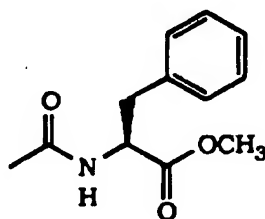


or a pharmaceutically acceptable salt or solvate thereof, wherein:

one of a, b, c and d represents N or NR⁹ wherein R⁹ is O⁻, -CH₃ or -(CH₂)_nCO₂H wherein n is 1 to 3, and the remaining a, b, c and d groups represent CR¹ or CR²; or

each of a, b, c, and d are independently selected from CR¹ or CR²;

each R¹ and each R² is independently selected from H, halo, -CF₃, -OR¹⁰, -COR¹⁰, -SR¹⁰, -S(O)_tR¹¹ (wherein t is 0, 1 or 2), -SCN, -N(R¹⁰)₂, -NR¹⁰R¹¹, -NO₂, -OC(O)R¹⁰, -CO₂R¹⁰, -OCO₂R¹¹, -CN, -NHC(O)R¹⁰, -NH₂SO₂R¹⁰, -CONHR¹⁰, -CONHCH₂CH₂OH, -NR¹⁰COOR¹¹, -SR¹¹C(O)OR¹¹,



-SR¹¹N(R⁷⁵)₂ (wherein each R⁷⁵ is independently selected from H and -C(O)OR¹¹), benzotriazol-1-yloxy, tetrazol-5-ylthio, or substituted tetrazol-5-ylthio, alkynyl, alkenyl or alkyl, said alkyl or alkenyl group optionally being substituted with halo, -OR¹⁰ or -CO₂R¹⁰;

R^3 and R^4 are the same or different and each independently represents H, any of the substituents of R^1 and R^2 , or R^3 and R^4 taken together represent a saturated or unsaturated C_5 - C_7 fused ring to the benzene ring;

- 5 R^5 , R^6 , R^7 and R^8 each independently represents H, $-CF_3$, $-COR^{10}$, alkyl or aryl, said alkyl or aryl optionally being substituted with $-OR^{10}$, $-SR^{10}$, $-S(O)_xR^{11}$, $-NR^{10}COOR^{11}$, $-N(R^{10})_2$, $-NO_2$, $-COR^{10}$, $-OCOR^{10}$, $-OCO_2R^{11}$, $-CO_2R^{10}$, OPO_3R^{10} or one of R^5 , R^6 , R^7 and R^8 can be taken in combination with R^{40} as defined below to represent $-(CH_2)_r$ wherein r is 1 to 4 which can be substituted with lower alkyl, lower alkoxy, $-CF_3$ or aryl, or R^5 is combined with R^6 to represent $=O$ or $=S$ and/or R^7 is combined with R^8 to represent $=O$ or $=S$;

R^{10} represents H, alkyl, aryl, or aralkyl;

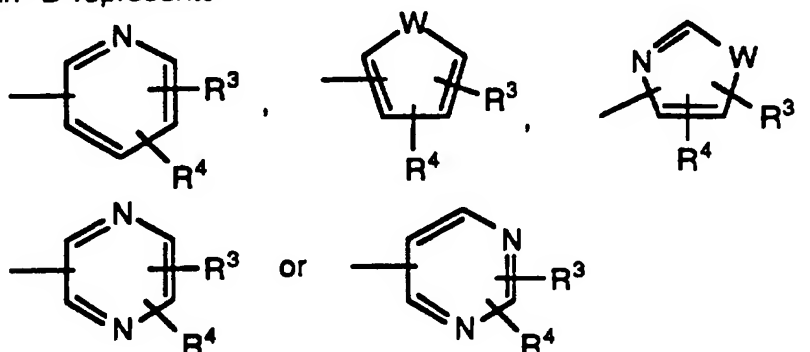
R^{11} represents alkyl or aryl;

- 15 X represents N, CH or C, which C may contain an optional double bond, represented by the dotted line, to carbon atom 11;

- the dotted line between carbon atoms 5 and 6 represents an optional double bond, such that when a double bond is present, A and B independently represent $-NO_2$, $-R^{10}$, halo, $-OR^{11}$, $-OCO_2R^{11}$ or
20 $-OC(O)R^{10}$, and when no double bond is present between carbon atoms 5 and 6, A and B each independently represent H_2 , $-(OR^{11})_2$, H and halo, dihalo, alkyl and H, $(alkyl)_2$, $-H$ and $-OC(O)R^{10}$, H and $-OR^{10}$, $=O$, aryl and H, $=NOR^{10}$ or $-O-(CH_2)_p-O-$ wherein p is 2, 3 or 4;

R represents R^{40} , R^{42} , R^{44} , or R^{54} , as defined below;

- 25 R^{40} represents H, aryl, alkyl, cycloalkyl, alkenyl, alkynyl or -D wherein -D represents



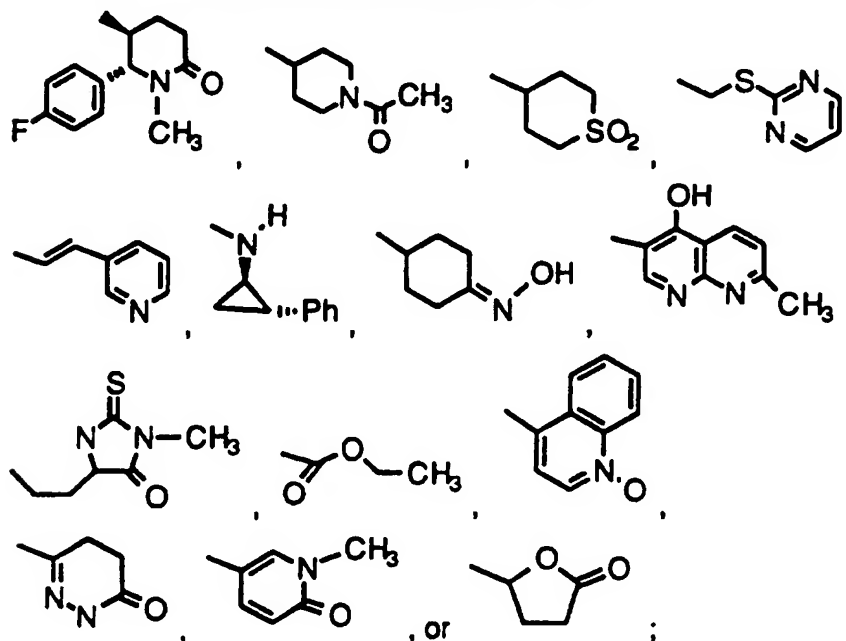
wherein R^3 and R^4 are as previously defined and W is O, S or NR^{10}

- wherein R^{10} is as defined above; said R^{40} cycloalkyl, alkenyl and alkynyl groups being optionally substituted with from 1-3 groups selected from
30 halo, $-CON(R^{10})_2$, aryl, $-CO_2R^{10}$, $-OR^{12}$, $-SR^{12}$, $-N(R^{10})_2$,

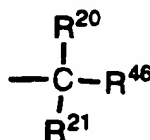
-N(R¹⁰)CO₂R¹¹, -COR¹², -NO₂ or D, wherein -D, R¹⁰ and R¹¹ are as defined above and R¹² represents R¹⁰, -(CH₂)_mOR¹⁰ or -(CH₂)_qCO₂R¹⁰ wherein R¹⁰ is as previously defined, m is 1 to 4 and q is 0 to 4; said alkenyl and alkynyl R⁴⁰ groups not containing -OH, -SH or

- 5 -N(R¹⁰)₂ on a carbon containing a double or triple bond respectively; or
 R⁴⁰ represents phenyl substituted with a group selected from
 -SO₂NH₂, -NHSO₂CH₃, -SO₂NHCH₃, -SO₂CH₃, -SOCH₃, -SCH₃, or
 -NHSO₂CF₃, preferably, said group is located in the para position of the
 phenyl ring; or

- 10 R⁴⁰ represents a group selected from



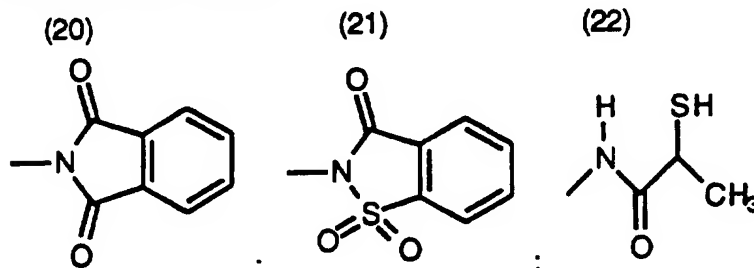
- 15 R⁴² represents



wherein R²⁰, R²¹ and R⁴⁶ are each independently selected from the group consisting of:

- (1) H;
 20 (2) -(CH₂)_qSC(O)CH₃ wherein q is 1 to 3;
 (3) -(CH₂)_qOSO₂CH₃ wherein q is 1 to 3;
 (4) -OH;
 (5) -CS(CH₂)_w(substituted phenyl) wherein w is 1 to 3 and the
 substituents on said substituted phenyl group are the same substituents
 25 as described below for said substituted phenyl;

- (6) $-NH_2$;
 (7) $-NHCBZ$;
 (8) $-NHC(O)OR^{22}$ wherein R^{22} is an alkyl group having from 1 to 5 carbon atoms, or R^{22} represents phenyl substituted with 1 to 3 alkyl groups;
 (9) alkyl;
 (10) $-(CH_2)_k$ phenyl wherein k is 1 to 6;
 (11) phenyl;
 (12) substituted phenyl wherein the substituents are selected from the group consisting of: halo, NO_2 , $-OH$, $-OCH_3$, $-NH_2$, $-NHR^{22}$, $-N(R^{22})_2$, alkyl, $-O(CH_2)_t$ phenyl (wherein t is from 1 to 3), and $-O(CH_2)_t$ substituted phenyl (wherein t is from 1 to 3);
 (13) naphthyl;
 (14) substituted naphthyl, wherein the substituents are as defined for substituted phenyl above;
 (15) bridged polycyclic hydrocarbons having from 5 to 10 carbon atoms;
 (16) cycloalkyl having from 5 to 7 carbon atoms;
 (17) heteroaryl;
 (18) hydroxyalkyl;
 (19) substituted pyridyl or substituted pyridyl N-oxide wherein the substituents are selected from methylpyridyl, morpholinyl, imidazolyl, 1-piperidiny, 1-(4-methylpiperazinyl), $-S(O)_tR^{11}$, or any of the substituents given above for said substituted phenyl, and said substituents are bound to a ring carbon by replacement of the hydrogen bound to said carbon;



- (23) $-NHC(O)-(CH_2)_k$ phenyl or $-NH(O)-(CH_2)_k$ substitued phenyl, wherein said k is as defined above;
 (24) piperidine Ring V:

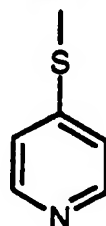
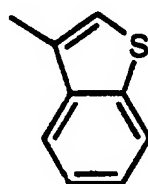
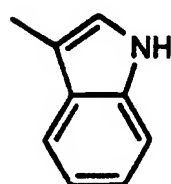


wherein R^{50} represents H, alkyl, alkylcarbonyl, alkyloxycarbonyl, haloalkyl, or $-C(O)NH(R^{10})$ wherein R^{10} is H or alkyl;

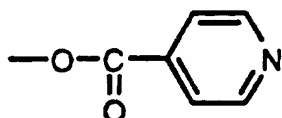
(25) $-NHC(O)CH_2C_6H_5$ or $-NHC(O)CH_2$ -substituted- C_6H_5 ;

5 (26) $-NHC(O)OC_6H_5$;

(27) (28) (29)



(30) $-OC(O)$ -heteroaryl, for example

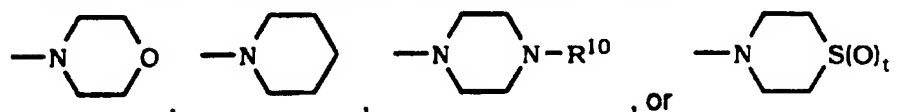


10 (31) $-O$ -alkyl (e.g., $-OCH_3$); and

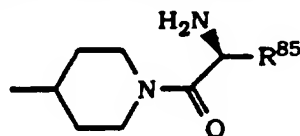
(32) $-CF_3$;

(33) $-CN$;

(34) a heterocycloalkyl group of the formula



15 (35) a piperidinyl group of the formula



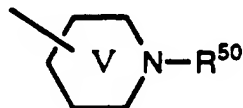
wherein R^{85} is H, alkyl, or alkyl substituted by $-OH$, $-SCH_3$ or $-SH$; and

(36) triazolyl; or

R^{20} and R^{21} taken together form a $=O$ group and the remaining

20 R^{46} is as defined above; or

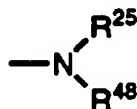
two of R^{20} , R^{21} and R^{46} taken together form piperidine Ring V



wherein R^{50} is as defined above;

with the proviso that R^{48} , R^{20} and R^{21} are selected such that the carbon atom to which they are bound does not contain more than one heteroatom;

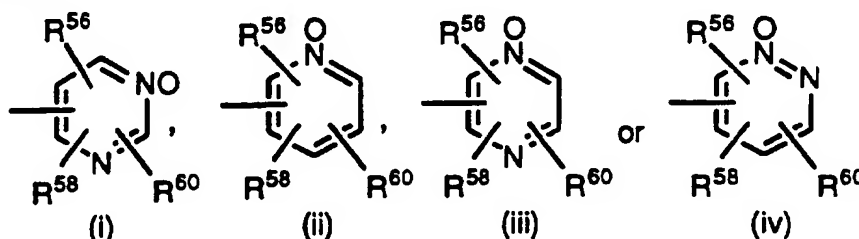
5 R^{44} represents



wherein R^{25} represents heteroaryl, N-methylpiperdiny or aryl; and R^{48} represents H or alkyl;

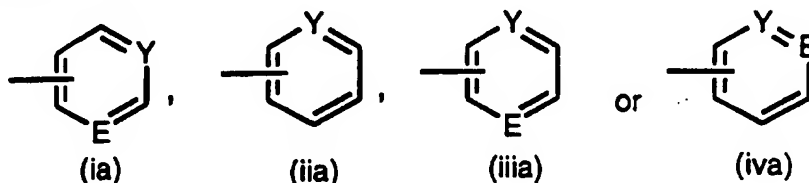
R^{54} represents an N-oxide heterocyclic group of the formula (i), (ii),

10 (iii) or (iv):



wherein R^{56} , R^{58} , and R^{60} are the same or different and each is independently selected from H, halo, $-\text{CF}_3$, $-\text{OR}^{10}$, $-\text{C}(\text{O})\text{R}^{10}$, $-\text{SR}^{10}$, $-\text{S}(\text{O})_e\text{R}^{11}$ (wherein e is 1 or 2), $-\text{N}(\text{R}^{10})_2$, $-\text{NO}_2$, $-\text{CO}_2\text{R}^{10}$, $-\text{OCO}_2\text{R}^{11}$, $-\text{OCOR}^{10}$, alkyl, aryl, alkenyl or alkynyl, which alkyl may be substituted with $-\text{OR}^{10}$, $-\text{SR}^{10}$ or $-\text{N}(\text{R}^{10})_2$ and which alkenyl may be substituted with OR^{11} or SR^{11} ; or

R^{54} represents an N-oxide heterocyclic group of the formula (ia), (iia), (iiia) or (iva):



wherein Y represents N^+-O^- and E represents N; or

R^{54} represents an alkyl group substituted with one of said N-oxide heterocyclic groups (i), (ii), (iii), (iv), (ia), (iia), (iiia) or (iva); and

Z represents O or S such that R can be taken in combination with R^5 , R^6 , R^7 or R^8 as defined above, or R represents R^{40} , R^{42} , R^{44} or R^{54} ;

with the proviso that when:

(1) R^1 , R^2 , R^3 and R^4 are independently selected from H, halo, $-\text{CF}_3$, $-\text{OR}^{10}$, $-\text{COR}^{10}$, $-\text{SR}^{10}$, $-\text{S}(\text{O})_e\text{R}^{11}$, $-\text{N}(\text{R}^{10})_2$, $-\text{NO}_2$, $-\text{OC}(\text{O})\text{R}^{10}$,

-CO₂R¹⁰, -OCO₂R¹¹, -CN, -NR¹⁰COOR¹¹, -SR¹¹C(O)OR¹¹,
 -SR¹¹N(R⁷⁵)₂, benzotriazol-1-yloxy, tetrazol-5-ylthio, substituted tetrazol-
 5-ylthio, alkynyl, alkenyl or alkyl; or R¹ and R² are selected from H, halo,
 -CF₃, -OR¹⁰, -COR¹⁰, -SR¹⁰, -S(O)_tR¹¹, -N(R¹⁰)₂, -NO₂, -OC(O)R¹⁰,
 5 -CO₂R¹⁰, -OCO₂R¹¹, -CN, -NR¹⁰COOR¹¹, -SR¹¹C(O)OR¹¹,
 -SR¹¹N(R⁷⁵)₂, benzotriazol-1-yloxy, tetrazol-5-ylthio, substituted tetrazol-
 5-ylthio, alkynyl, alkenyl or alkyl, and R³ and R⁴ taken together represent
 a saturated or unsaturated C₅-C₇ fused ring to the benzene ring (Ring III);
 and

10 (2) the dotted line between carbon atoms 5 and 6 represents
 an optional double bond, such that when a double bond is present, A and
 B independently represent -R¹⁰, halo, -OR¹¹, -OCO₂R¹¹ or -OC(O)R¹⁰,
 and when no double bond is present between carbon atoms 5 and 6, A
 and B each independently represent H₂, -(OR¹¹)₂, H and halo, dihalo,
 15 alkyl and H, (alkyl)₂, -H and -OC(O)R¹⁰, H and -OR¹⁰, =O, aryl and H,
 =NOR¹⁰ or -O-(CH₂)_p-O- wherein p is 2, 3 or 4;

then R is selected from:

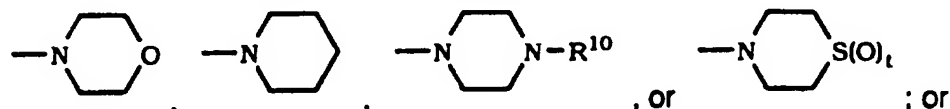
(a) R⁴² wherein at least one of R²⁰, R²¹ or R⁴⁶ is selected
 from:

20 (1) substituted pyridyl or substituted pyridyl N-oxide wherein
 the substituents are selected from methylpyridyl, morpholiny, imidazolyl,
 1-piperidiny, 1-(4-methylpiperaziny), or -S(O)_tR¹¹;

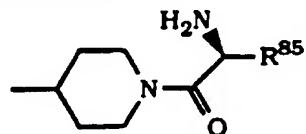
(2) -CN;

(3) triazolyl;

25 (4) a heterocycloalkyl group of the formula



(5) a piperidiny group of the formula




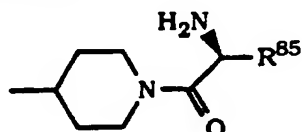
wherein R⁸⁵ is H, alkyl, or alkyl substituted by -OH, -SCH₃ or -SH; or

30 (b) R⁴⁴ wherein R²⁵ is N-methylpiperidiny.

2. The method of Claim 1 wherein a is N and b, c, and d are
 carbon; R¹ and R² are the same or different and each is independently
 selected from H, halo, -CF₃, lower alkyl, or benzotriazol-1-yloxy, and R¹ is

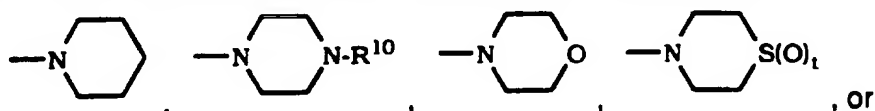
at the C-4 position and R² is at the C-3 position; R³ and R⁴ are the same or different and each is independently selected from H or halo, and R³ is at the C-8 position and R⁴ is at the C-9 position; when the double bond between carbon atoms 5 and 6 is present, A and B independently represent H, lower alkyl or alkyloxy; and when the double bond between carbon atoms 5 and 6 is absent, A and B independently represent H₂, (-H and -OH) or =O; R⁵, R⁶, R⁷, and R⁸ are H; Z is O; and R represents R⁴² and the R⁴⁶ is selected from: (1) -CN; triazolyl; (2) a heterocycloalkyl group of the formula

10  ; (3) a piperidiny group of the formula

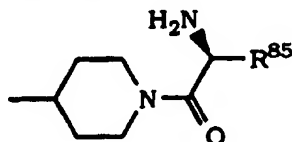


wherein R⁸⁵ is H, alkyl, or alkyl substituted by -OH or -SCH₃; or (4) substituted pyridyl or substituted pyridyl N-oxide wherein the substituents
15 are selected from methylpyridyl, morpholinyl, imidazolyl, 1-piperidinyl, 1-(4-methylpiperazinyl), or -S(O)_tR¹¹.

3. The method of Claim 2 wherein R²⁰ and R²¹ are each independently selected from H and alkyl; R³ is Cl; R⁴ is H; R¹ and R² are individually selected from H, benzotriazol-1-yloxy, C₁ to C₄ alkyl or halo; and R⁴⁶ represents triazolyl, a heterocycloalkyl of the formula

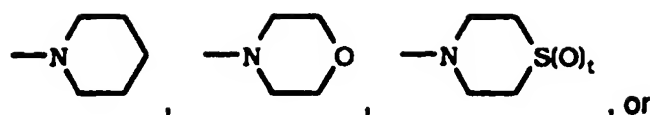


a piperidinyl group of the formula

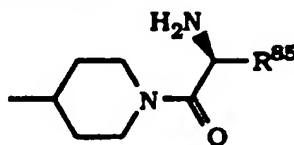


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4. The method of Claim 3 wherein both R²⁰ and R²¹ are H, or both R²⁰ and R²¹ are methyl; R¹ and R² are individually selected from H, Br, Cl, methyl or benzotriazol-1-yloxy; and R⁴⁶ represents triazolyl, 1-N-methylpiperazinyl, 1-piperazinyl, a heterocycloalkyl of the formula



a piperidiny group of the formula



- 5 5. The method of Claim 1 wherein a is N and b, c, and d are carbon; R¹ and R² are the same or different and each is independently selected from H, halo, -CF₃, lower alkyl, or benzotriazol-1-yloxy, and R¹ is at the C-4 position and R² is at the C-3 position; R³ and R⁴ are the same or different and each is independently selected from H or halo, and R³ is at the C-8 position and R⁴ is at the C-9 position; when the double bond between carbon atoms 5 and 6 is present, A and B independently represent H, lower alkyl or alkyloxy; and when the double bond between carbon atoms 5 and 6 is absent, A and B independently represent H₂, (-H and -OH) or =O; R⁵, R⁶, R⁷, and R⁸ are H; Z is O; and R represents R⁴⁴ and the R²⁵ represents, 3-N-methylpiperidiny or 4-N-methylpiperidiny.

- 20 6. The method of Claim 5 wherein R³ is Cl; R⁴ is H; R⁴⁸ represents are H or methyl; and R¹ and R² are individually selected from H, benzotriazol-1-yloxy, methyl, Br or Cl.

- 25 7. The method of Claim 1 wherein the the cells inhibited are tumor cells expressing an activated ras oncogene.

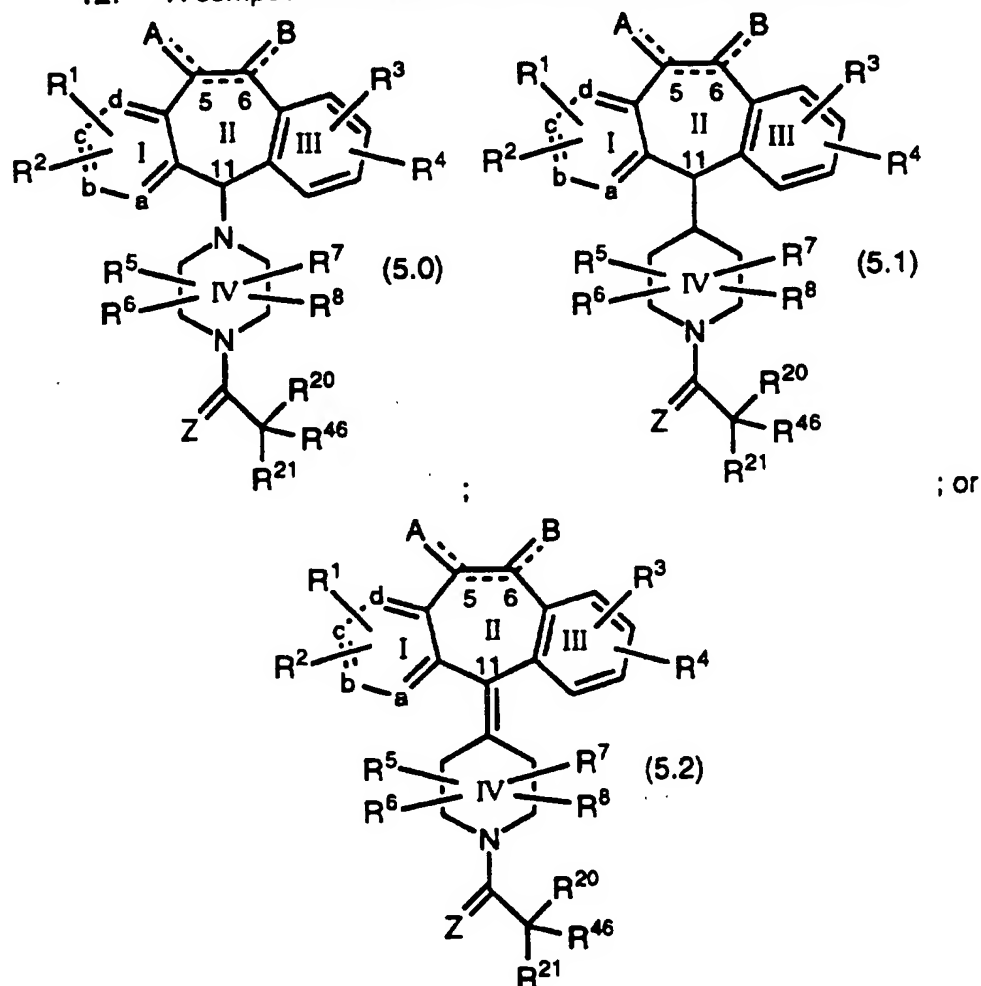
- 30 8. The method of Claim 7 wherein the cells inhibited are pancreatic tumor cells, lung cancer cells, myeloid leukemia tumor cells, thyroid follicular tumor cells, myelodysplastic tumor cells, epidermal carcinoma tumor cells, bladder carcinoma tumor cells or colon tumors cells.

9. The method of Claim 1 wherein the inhibition of the abnormal growth of cells occurs by the inhibition of farnesyl protein transferase.

10. The method of Claim 1 wherein the inhibition is of tumor cells wherein the Ras protein is activated as a result of oncogenic mutation in genes other than the Ras gene.

5 11. The method of Claim 1 wherein the compound is selected from the compounds of Examples: 426, 400-G, 400-C, 400-F, 400-E, 425-H, 401, 400-B, 400, 400-L, 425-U, 413, 400-J, 417-B, 438, 411-W, 425-O, 400-D, 400-K, 410-G or 400-H.

10 12. A compound selected from a compound of the formula:

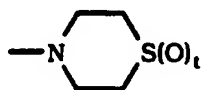


or a pharmaceutically acceptable salt or solvate thereof, wherein all the substituents are as defined in Claim 1.

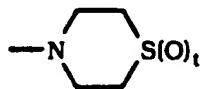
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13. The compound of Claim 12 wherein a is N and b, c, and d are carbon; R¹ and R² are the same or different and each is

- independently selected from H, halo, $-CF_3$, lower alkyl, or benzotriazol-1-yloxy, and R^1 is at the C-4 position and R^2 is at the C-3 position; R^3 and R^4 are the same or different and each is independently selected from H or halo, and R^3 is at the C-8 position and R^4 is at the C-9 position; when the double bond between carbon atoms 5 and 6 is present, A and B independently represent H, lower alkyl or alkyloxy; and when the double bond between carbon atoms 5 and 6 is absent, A and B independently represent H_2 , $(-H$ and $-OH)$ or $=O$; R^5 , R^6 , R^7 , and R^8 are H; Z is O; and R^{46} is selected from triazolyl, 1-N-methylpiperazinyl, 1-piperazinyl or a heterocycloalkyl of the formula

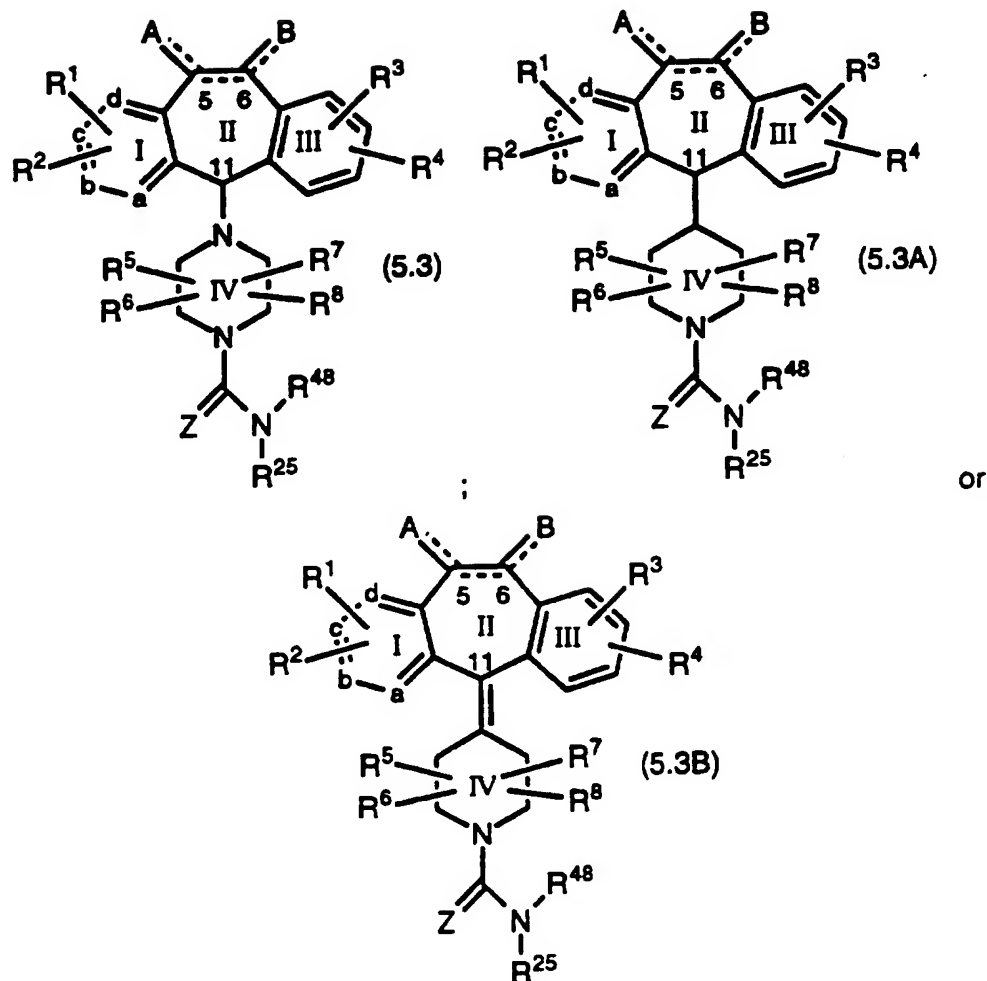


14. The compound of Claim 13 wherein R^{20} and R^{21} are each independently selected from H and alkyl; R^3 is Cl; R^4 is H; R^1 and R^2 are individually selected from H, benzotriazol-1-yloxy, C_1 to C_4 alkyl or halo; and R^{46} represents 1-N-methylpiperazinyl, 1-piperazinyl or a heterocycloalkyl of the formula



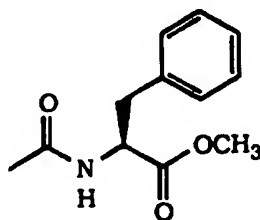
15. The compound of Claim 14 wherein both R^{20} and R^{21} are H, or both R^{20} and R^{21} are methyl; and R^1 and R^2 are individually selected from H, Br, Cl, methyl or benzotriazol-1-yloxy.

16. A compound selected from a compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein a, b, c, d, R⁵, R⁶, R⁷, R⁸, A, B and Z are as defined in Claim 1;

- 5 each R¹ and each R² is independently selected from H, halo, -CF₃, -OR¹⁰, -COR¹⁰, -SR¹⁰, -S(O)_tR¹¹ (wherein t is 0, 1 or 2), -SCN, -N(R¹⁰)₂, -NR¹⁰R¹¹, -NO₂, -OC(O)R¹⁰, -CO₂R¹⁰, -OCO₂R¹¹, -CN, -NHC(O)R¹⁰, -NHSO₂R¹⁰, -CONHR¹⁰, -CONHCH₂CH₂OH, -NR¹⁰COOR¹¹, -SR¹¹C(O)OR¹¹,



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-SR¹¹N(R⁷⁵)₂ (wherein each R⁷⁵ is independently selected from H and -C(O)OR¹¹), benzotriazol-1-yloxy, tetrazol-5-ylthio, or substituted tetrazol-

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5-ylthio, alkynyl, alkenyl or alkyl, said alkyl or alkenyl group optionally being substituted with halo, $-OR^{10}$ or $-CO_2R^{10}$;

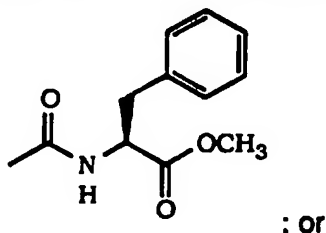
R^3 and R^4 are the same or different and each independently represents H, any of the substituents of R^1 and R^2 , or R^3 and R^4 taken together represent a saturated or unsaturated C_5 - C_7 fused ring to the benzene ring;

R^{25} represents heteroaryl, N-methylpiperidinyl or aryl; and

R^{48} represents H or alkyl; and

with the proviso that:

(1) when R^{25} is selected from heteroaryl or aryl then: (a) at least one of said R^1 , R^2 , R^3 and R^4 groups is selected from $-SCN$, $-NR^{10}R^{11}$, $-NHC(O)R^{10}$, $-NHSO_2R^{10}$, $-CONHR^{10}$, $-CONHCH_2CH_2OH$, or



(b) the double bond between carbon atoms 5 and 6 is present and at least one of A and B represents $-NO_2$; and

(2) when R^{25} is N-methylpiperidinyl selected from 3-N-methylpiperidinyl or 4-N-methylpiperidinyl then R^1 and R^2 are not H, halo, $-CF_3$, benzotriazol-1-yloxy or lower alkyl when: (a) R^3 and R^4 are selected from H and halo; and (b) the double bond between carbon atoms 5 and 6 is present and A and B are selected from H, lower alkyl or lower alkoxy, or the double bond between carbon atoms 5 and 6 is absent and A and B are selected from H_2 , $(-H$ and $-OH)$ or $=O$; and (c) R^5 , R^6 , R^7 , and R^8 are H; and (d) Z is O.

17. A compound selected from a compound having the structure number: 5.200, 5.201, 5.202, 5.203, 5.204, 5.205, 5.206, 5.207, 5.208, 5.209, 5.210, 5.211, 5.212, 5.213, 5.214, 5.215, 5.216, 5.217, 5.218, 5.219, 5.220.

18. A compound selected from the compounds of Examples: 400-A, 400-M, 400-N, 400-P, 400-Q, 402, 402-A, 403, 404, 405, 406, 407, 410-H, 410-J, 410-L, 410-M, 410-Q, 410-R, 410-S, 410-T, 410-U, 410-V, 410-W, 410-X, 411, 411-A, 411-B, 411-C, 411-D, 411-E, 411-F, 411-G,

411-H, 411-J, 411-K, 411-L, 411-M, 411-N, 411-O, 411-P, 411-Q, 411-R,
411-S, 411-T, 411-U, 411-V, 411-X, 411-Z, 411-AA, 411-BB, 411-CC,
411-DD, 411-EE, 411-FF, 411-GG, 412, 412-A, 412-B, 412-C, 412-D,
412-E, 412-F, 412G, 412-H, 414, 414-A, 414-B, 415, 416, 417, 417-A,
5 418, 419, 420, 421, 422, 422-A, 423, 423-A, 423-B, 424, 424-A, 425, 425-
A, 425-B, 425-C, 425-D, 425-E, 425-F, 425-G, 425-J, 425-K, 425-L, 425-
M, 425-N, 425-P, 425-Q, 425-R, 425-S, 425-T, 425-V, 426-A, 427, 427-A,
427-B, 427-C, 428, 428-A, 429, 430, 430-A, 431, 431-A, 431-B, 431-C,
431-D, 431-E, 431-F, 431-G, 432, 433, 433-A, 433-B, 433-C, 434, 434-A,
10 435, 436, 436-A, 436-B, 436-C, 436-D, 437, 438-A, 438-B, 439, 440, 440-
A, 441, 500, 501, 502, 503, 504, 505, 506, 507 or 508.

19. A pharmaceutical composition for inhibiting the abnormal
growth of cells comprising an effective amount of a compound of any of
15 Claims 12, 16 or 18 in combination with a pharmaceutically acceptable
carrier.

20. The use of a compound of any of Claims 12, 16 or 18 for the
manufacture of a medicament for use in inhibiting the abnormal growth of
20 cells.

21. The use of a compound of any of Claims 12, 16 or 18 for
inhibiting the abnormal growth of cells.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/03314

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D401/04 A61K31/445 C07D401/14 C07D401/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 270 818 (SCHERING CORP) 15 June 1988 see claims ---	12-19
X	EP,A,0 396 083 (SCHERING CORP) 7 November 1990 see claims ---	12-19
A	WO,A,92 11034 (WELLCOME FOUND) 9 July 1992 cited in the application see the whole document ---	1-20
P,X	WO,A,95 10516 (SCHERING CORP) 20 April 1995 see claims -----	1-20

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

9 July 1996

Date of mailing of the international search report

17. 07. 96

Name and mailing address of the ISA

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Authorized officer

Henry, J

INTERNATIONAL SEARCH REPORT

International application No.

PLT/US 96/03314

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 1-11 and 21 are aligned to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the compounds.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 96/03314

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0270818	15-06-88	US-A- 4826853	02-05-89
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		AU-B- 7285991	30-05-91
		AU-B- 604285	13-12-90
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 96/03314

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